AR201-13108

E. I. du Pont de Nemours & Co., Inc.
1007 Market Street
Wilmington, DE 19898

Christine Todd Whitman, Administrator
US EPA
P.O. Box1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

Dear Administrator Whitman:

E. I. du Pont de Nemours & Co., Inc. and Solutia Inc are pleased to submit the proposed test plan along with the robust summaries for the chemical category designated the "dicarboxylic acid category". Dicarboxylic acids included in this group are succinic acid (110-15-6), glutaric acid (110-94-1) and adipic acid (124-04-9).

We will not begin action on this test plan until the comment period has expired and submitted remarks have been reviewed.

This submission includes one electronic copy in .pdf format. Hard copy can be provided upon request. The EPA registration number for the consortium is , and the internal agency tracking number on the EPA website is 201-12754.

Please feel free to contact me with any questions or concerns you might have concerning the submission at kathleen.e.lanshe@usa.dupont.com or 302-992-3826.

Sincerely

E. I. du Pont de Nemours & Company, Inc:

Kathleen E. Lanshe
Occupational Health Consultant

Solutia Inc:

Robert A. Barter, Ph.D., DABT
Manager, Product Stewardship and Toxicology

AR201-13108A

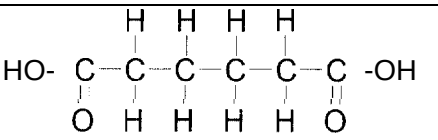
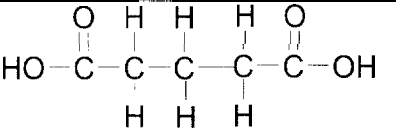
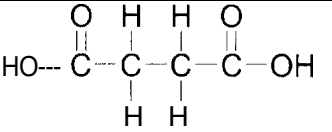
10-July-2001

ROBUST SUMMARY FOR DICARBOXYLIC ACID CATEGORY

Summary

Identification of a structure based category

The alkane dicarboxylic acid category is composed of linear alkanes with a common function group, carboxylic acid, at each end of the alkane chain. This category is composed of discrete materials that change by an increase in carbon number from an addition of CH_2 in the alkane chain between the carboxylic acid groups. The total carbon chain length is between four and six carbons. Dicarboxylic acids included in this group are succinic acid (C4), glutaric acid (C5), and adipic acid (C6). Structures of these acids are presented below.

Chemical Name	CAS Registry Number	Structure
Hexanedioic acid (Adipic Acid)	124-04-9	
Pentanedioic acid (Glutaric Acid)	110-94-1	
Butanedioic acid (Succinic Acid)	110-15-6	

The terminal carboxylic acids and limited chain length provide similar structure activity relationships with these materials. The boundaries for this category were placed on C4 to C6 dicarboxylic acids, as these materials are products of adipic acid manufacture from cyclohexanol. In addition to information on the discrete materials, data exists and will be presented on a mixture of the dicarboxylic acids (AGS mixture) to lend overall support to the alkane dicarboxylic acid category. Finally, in the data summaries information will be presented that indicate these materials share similar physical chemical properties, environmental fate characteristics, ecotoxicity, and mammalian toxicity.

Scientific literature was searched and summarized. Data were identified for materials in the category, as well as data on the mixture of member materials (Table 1). A majority of the SIDS endpoints were covered for the individual materials, as well as the category. Each study on category materials was evaluated for adequacy. Robust summaries were developed for each study addressing specific SIDS endpoints. Summaries were also developed for studies either considered not adequate but provided information of

relevance for hazard identification and evaluation, or covered non-SIDS endpoints (Appendices A-D).

Table 1: Matrix of Available and Adeauate Data for Dicarboxvlic Acid Category

	Adipic Acid	Glutaric Acid	Succinic Acid	AGS Mixture
PHYSICAL/CHEMICAL CHARACTERISTICS				
Melting Point	√	√	√	√
Boiling Point	√		√	√
Vapor Pressure	√	√	√	√
Partition Coefficient	√		√	–
Water Solubility	√	√	√	√
ENVIRONMENTAL FATE				
Photodegradation	√	√	√	–
Stability in Water	√	√		–
Transport (Fugacity)	√	√	√	
Biodegradation		√		√
ECOTOXICITY				
Acute Toxicity to Fish	√	√/–	√/–	√
Acute Toxicity to Invertebrates	√		√	√
Acute Toxicity to Aquatic Plants	√	√/–	√/–	√
MAMMALIAN TOXICITY				
Acute Toxicity	√	√	√	√
Repeated Dose Toxicity	√	√	√	√
Developmental Toxicity	√	√	–	–
Reproductive Toxicity	–		–	–
Genetic Toxicity Gene Mutations	√	√	√	√
Genetic Toxicity Chromosomal Aberrations	√	√	√	√

√ = Data are available and considered adequate.
= No data available.
√/– = Data are available, but considered inadequate.

Evaluation of Data Matrix Patterns

The available adequate data were broken out by discipline (physical chemical, environmental fate, ecotoxicology, and mammalian toxicology). These comparisons were conducted to determine if a pattern existed among the materials and to determine if additional testing needed to be conducted to complete the data set for the category. In general, the most striking pattern across the group of materials is their low toxicity. This applies to both mammalian species, as well as aquatic organisms.

All three alkane dicarboxylic acids have roughly equivalent physical chemical properties (Table 2). Further these properties follow a general trend with succinic acid (C4) having a lower boiling point, vapor pressure, and Kow, and higher density, melting point, and water solubility than adipic acid (C6). Glutaric acid has physical chemical properties that generally fall within the values for succinic and adipic acids. Thus a true trend for the alkane dicarboxylic acid category exists.

Table 2: Physical and Chemical Characteristics

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Physical Appearance	White, odorless, crystalline powder	White crystalline solid	Colorless to white crystalline powder, odorless to carmel odor	Off-white solid, with a pungent odor
Molecular Weight	146.14	132.13	118.09	Not Applicable
Water Solubility	30 g/L at 30°C	1600 g/L at 28°C	83 g/L at 25°C	350 g/L at 25°C
Melting Point	152°C	97.5-98°C	185-187°C	1 oo-130°C
Boiling Point	330.5°C	302-304°C	235°C	300-330°C
Vapor Pressure	$3.18x10^{-7}$ mm Hg at 25°C	$2.88x10^{-6}$ mm Hg at 25°C	$1.9x10^{-7}$ mm Hg at 25°C	4 mm Hg at 160°C
Density	1.360 at 25°/4°C	1.429 at 15°/4°C	I.564 at 15°/4°C	1.23 at 20°C
Partition Coefficient (log Kow)	0.08 1	-0.29	-0.59	No Data

Ecotoxicity data are essentially equivalent for the category members (Table 3). The environmental fate data indicate all materials are readily biodegradable and do not bioaccumulate. Fugacity model prediction for the alkane dicarboxylic acids indicate these materials will act similarly in regards to partitioning in the environment. Modeled data shows that all 3 test materials are essentially the same in terms of partitioning, with more material partitioning to the soil, and to a slightly lesser extent to water: with virtually none going to air or sediment.

Table 3: Ecotoxicity

	Adipic Acid	Glutaric Acid	Succinic Acid	Dicarboxylic Acid Mixture
Bioaccumulation	Low BCF = 0.68	Low BCF = 3.162	Low BCF = 0.21	No Data
Biodegradation	Readily Biodegradable	Readily Biodegradable	Readily Biodegradable	Readily Biodegradable
Fugacity*	Air <0.001% Water 42.4% Soil 57.5% Sediment *0.06%*	Air <0.001% Water 42.6% Soil 57.3% Sediment *0.064%*	Air <0.001% Water 42.7% Soil 57.2% Sediment *0.06%*	No Data

* Modeled data.

Aquatic toxicity of the alkane dicarboxylic acid category is generally low (Table 4). Acute toxicity to fish for adipic and glutaric acids are similar. Data for succinic acid, although not definitive, indicate that the LC_{50} for succinic acid is in the same general order. This conclusion is also supported by data generated for the mixture of the three dicarboxylic acids. Information with *Duphnia* indicate results for adipic and succinic acids in the same order of magnitude. Finally, acute toxicity to algae indicate that dicarboxylic acids have similar toxicity in these organisms.

Table 4: Aquatic Toxicity

	Adipic Acid	Glutaric Acid	Succinic Acid	Dicarboxylic Acid Mixture
Toxicity to Fish (LC_{50} value)	*97* mg/L (96-hour)	*330* mg/L (24-hour)	>15 ppm (24-hour)	*240-340* mg/L (96-hour)
Toxicity to Invertebrates (EC_{50} value)	*85.7* mg/L (48-hour)	No Data	*374.2* mg/L (48-hour)	>1000 mg/L (48-hour)

Toxicity to Algae (EC_{50} value)	26.6 mg/L (96-hour)	264 mg/L (72-hour)	120 mg/L	35 mg/L (96-hour)

In mammalian species the low toxicity is manifest in high lethal doses in acute studies, limited toxicity (body weight effects) in repeat dose studies, and no effects in teratologic evaluations (Tables 5 and 6). This is not unexpected as succinic acid is a component of carbohydrate metabolism in living systems, and the FDA regulates adipic acid as a GRAS (generally recognized as safe) component. It appears that the LD_{50} may be influenced by chain length as the C4 dicarboxylic acid, succinic acid, has a lower LD_{50} than glutaric (C5) and adipic (C6) acids. A similar relationship also exists in ocular irritation, where severity of response decreases with increasing carbon number. When tested in rabbits, adipic acid produced slight to mild skin irritation, and glutaric and succinic acids produced slight skin irritation. When tested in guinea pigs the mixture produced no to mild skin irritation. In dermal sensitization studies in guinea pigs, adipic acid and the mixture of the acids did not produce skin sensitization.

Table 5: Acute Mammalian Toxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Oral LD_{50} (rat)	5050 mg/kg	2750 mg/kg	2260 mg/kg	6829 mg/kg
Inhalation LC_{50} (rat)	> 7.7 mg/L	No Data	No Data	>0.03 mg/L
Dermal LD_{50} (rabbit)	> 7940 mg/kg	> 10,000 mg/kg	No Data	> 7940 mg/kg
Dermal Irritation	Slight to mild	Slight	Slight	No to mild
Eye Irritation	Mild to moderate	Moderate	Severe	Mild to severe
Dermal Sensitization	Not a sensitizer	No Data	No Data	Not a sensitizer

Repeated exposure studies in rats with adipic acid (2 years), glutaric acid (90 days), and succinic acid (90 days and 2 years, tested as the sodium salt, which is appropriate since on contact with water in living systems it dissociates to the acid form), as well as the mixture of the acids (90 days), have indicated a low degree of toxicity. A low degree of toxicity was also seen in a repeated exposure study (90 days) with glutaric acid in dogs. Concentrations of 1-2% of the individual acids, and 3% of the acid mixture were well

tolerated. Higher concentrations of all 4 test substances were associated with a depressed rate of weight gain. No specific target organ was identified for any of the individual acids or the AGS mixture.

Developmental toxicity studies have been conducted for glutaric and adipic acids in both rat and rabbit (Table 6). These studies resulted in no adverse effects on pregnancy and no embryotoxic or teratogenic effects. It is reasonable to assume that this category does not pose a developmental toxicity hazard.

Evaluation of reproductive toxicity for the alkane dicarboxylic acid category cannot be conducted with currently available data (Table 6). No studies have been conducted to examine the effects of any of these materials on male or female fertility. Histopathological evaluations of the gonads were conducted in some of the repeated dose studies, but were not sufficient to eliminate the possibility of an effect. Based on the similarity of results in acute and repeated dose studies for the alkane dicarboxylic acids, it is anticipated that effects on fertility would be similar. As such it is proposed to evaluate the reproductive effects of adipic acid in an OECD Guideline 422 reproductive toxicity screen.

Table 6: Repeated Dose, Developmental, and Reproductive Toxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Repeated Dose Toxicity (NOAEL)	1% in a 2-year study	1-2% in a 90-day study	1.25% in a 90-day study 1% in a 2-year study	3% in a 90-day study
Developmental Toxicity	Not teratogenic	Not teratogenic	No reliable data	No Data
Reproductive Toxicity	No effect on reproductive organs in repeated exposure studies	No effect on reproductive organs in repeated exposure studies	No reliable data	No effect on reproductive organs in a repeated exposure study

Genetic toxicity data are similar between the three acids, supporting a category approach (Table 7). Neither succinic, glutaric, nor adipic acids induce mutations in bacteria, as is the case with the mixture. Similar responses were seen with the 3 diacids and clastogenic activity. Adipic acid was inactive *in vitro* and *in vivo*. Succinic acid was inactive *in vitro;* glutaric was inactive *in vivo*, and essentially inactive *in vitro* (2 assays reported negative results and 1 assay reported positive results). It can be reasonably assumed that succinic acid will be inactive *in vivo* and glutaric inactive *in vitro.* The mixture of the

acids was inactive in point mutations assays in *Salmonella,* unscheduled DNA synthesis (UDS) in rat hepatocytes, and in the HGPRT assay. Somewhat surprisingly, the mixture of the acids was genotoxic in an in *vitro* Chinese hamster ovary (CHO) clastogenicity study. The reason for this response is not known. The mixture was, however, inactive *in vivo.* Taken collectively, it can be concluded that these test substances are inactive for mutagenic and clastogenic effects.

Table 7: Genetic Toxicity

	Adipic Acid	Glutaric Acid	Succinic Acid	Dicarboxylic Acid Mixture
Mutagenic	**No**	**No**	**No**	**No**
Clastogenic	**No**	**No**	**No**	**No**

Overall, the toxicologic database for the individual acids and the mixture is relatively complete, and the information available does not suggest a high level of concern. The database could be enhanced by investigating reproductive toxicity. Table 8 lists the proposed test plan for the dicarboxylic acid category. The shaded cells represent those SIDS endpoints for which testing was recommended.

Table 8: Alkane Diacids Proposed SIDS Test Plan

	Adipic Acid	Glutaric Acid	Succinic Acid	AGS Mixture
Reproductive Assessment	-	-*	-*	

- = No data available.
* = Evaluation of the test substance will be considered based upon the results obtained from the study performed with adipic acid.

Once the reproductive screen on adipic acid is completed the results will indicate if additional testing is needed. If no adverse effects on reproductive function are determined, no additional testing will be conducted. If reproductive function is adversely affected, succinic/glutaric acids will be considered for evaluation to determine if these effects occur across the entire range of alkane dicarboxylic acids.

Exposure Assessment

Dibasic Acid (DBA) is a by-product manufactured in the production of adipic acid at several domestic and regional facilities. Glutaric and succinic acids are non-commercialized by-products of this process. Approximately 94% of the volume of DBA produced is as adipic acid. Approximately 4.25% of the dibasic acid mixture is converted to dibasic esters by esterification of the acid moieties with methanol, either on site or by toll manufacturers. Approximately 1.2% of the DBA production is burned as

fuel at manufacturing sites and the remaining 0.55% is sold to customers or distributors for use as corrosion inhibitors and as a pH buffer for lime and limestone SO_2 scrubbers. All sites that produce and use DBA have safety, health, & environmental practices and procedures in place and utilize engineering controls, environmental controls, and personal protective equipment to manage the risk of exposure above recommended limits. The toll manufactures also have procedures, practices, and controls in place to manage the risk of exposure, and no sites or customers have reported any SHE incidents from the handling of DBA. The major manufacturers of DBA practice Responsible Care@ and assess the ability of potential toll manufacturers and customers to safely handle DBA prior to commencing a commercial relationship. This assessment includes reviews and audits of PPE (personal protective equipment), safety equipment and procedures, structural integrity, and safety practices.

DBAs are primarily the by product of commercial production of adipic acid, an industrial intermediate for the production of Nylon 6,6 for use in fibers, engineering resins, films, and monofiliments. Other applications for adipic acid include flue gas desulphurization, adhesives, and food additives. Adipic acid is generally recognized as safe (GRAS) under 2 1 CFR 184.1009 when used in foods at levels not to exceed current good manufacturing practice in accordance with 2 1 CFR 184. lb 1.

Concerns with adipic acid focus on physical handling of the product. When dispersed as a dust, adipic acid is subject to normal dust explosion hazards. The minimum ignition energy (MIE), a measure of dust explosivity, is 5 mJ. Tests show that unloading 907 kg (2000 lb) bulk bags of adipic acid can generate voltage levels necessary to constitute a spark hazard. The major producers of adipic acid practice Responsible Care@ and follow its distribution management practice.

The sites handling DBA and adipic acid can have from 250 to 2000 personnel (construction, contractor, and plant employees). The area where the substances are manufactured will have from 2 to 5 operators during normal operations and from 10 to 60 people during a shutdown or major construction activity. The DuPont Acceptable Exposure Limit for adipic acid is 5 mg/m^3, 8- and 12-hour TWA. The ACGIH Threshold Limit Value is 5 mg/m^3, 8-hour TWA, and the Workplace Environmental Exposure Level is 5 mg/m^3, 15-minute TWA. OSHA has not established a Permissible Exposure Limit.

Exposure Groups

Data are presented below on various occupational exposures to alkane dicarboxylic acids. As the majority of alkane dicarboxylic acids are produced as site limited intermediates, exposure to these materials are limited. Little exposure to adipic acid, glutaric acid, or succinic acid vapor occurs to manufacturing personnel. Exposure to adipic acid, the one alkane dicarboxylic acid with large commercial applications, during the loading of hopper cars and QA/QC in the process lab, is below exposure standards.

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Personal monitoring of DBA vapor samples were collected on silica gel tubes using a low flow pump. Adipic, glutaric and succinic acids were separated by ion exchange chromatography followed by FID detection.

Adipic acid dust TWA samples are collected gravimetrically using 0.8 micron pore sized mixed cellulose ester (MCE) filters that are matched-weighted to within 50 micrograms. Matched-weight refers to two filters that are matched in weight and loaded into a 37 mm cassette. The top filter collects contaminants and the bottom filter serves as a control. After sampling, both filters are removed and weighed; the difference between weights is the total dust sample weight. LOGAN (Lognormal Analysis) is used for characterizing employee exposure to chemicals. LOGAN predicts exposure for an entire group in a given workplace based on a limited number of samples. LOGAN maintains that employee risk of overexposure is less than 5%.

Occupational Exposure to Dicarboxylic Acid Vapor During Manufacture				
Chemical	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
Adipic Acid	14	0.10	0.02	0.58
Glutaric Acid	14	0.13	0.01	0.21
Succinic Acid	13	0.11	0.01	0.15

Exposure to Adipic Acid Dust During Loading Operations				
People	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
8	25	0.5832	0.01	4.1475
16	14	2.26	co.01	15.28

Exposure to Adipic Acid Dust by QA/QC Technical Personnel				
Chemical	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
16	3	0.10	co.01	0.20

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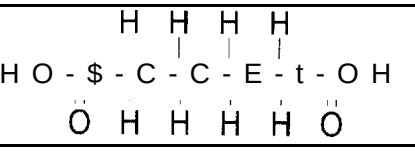
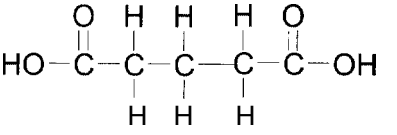
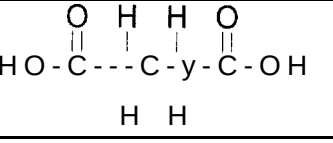
Hexanedioic acid (Adipic Acid)	124-04-9	
Pentanedioic acid (Glutaric Acid)	110-94-l	
Butanedioic acid (Succinic Acid)	110-15-6	

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Boiling Point	√		√	√
Vapor Pressure	√	√	√	√
Partition Coefficient	√		√	–
Water Solubility	√	√	√	√
ENVIRONMENTAL FATE				
Photodegradation	√	√	√	–
Stability in Water	√	√		–
Transport (Fugacity)	√	√	√	
Biodegradation		√		√
ECOTOXICITY				
Acute Toxicity to Fish	√	√/–	√/–	√
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Acute Toxicity to Aquatic Plants	√	√/–	√/–	√
MAMMALIAN TOXICITY				
Acute Toxicity	√	√	√	√
Repeated Dose Toxicity	√	√	√	√
Developmental Toxicity	√	√	–	–
Reproductive Toxicity	–		–	–
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Genetic Toxicity Chromosomal Aberrations	√	√	√	√

√ = Data are available and considered adequate.
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Evaluation of Data Matrix Patterns

The available adequate data were broken out by discipline (physical chemical, environmental fate, ecotoxicology, and mammalian toxicology). These comparisons were conducted to determine if a pattern existed among the materials and to determine if additional testing needed to be conducted to complete the data set for the category. In general, the most striking pattern across the group of materials is their low toxicity. This applies to both mammalian species, as well as aquatic organisms.

All three alkane dicarboxylic acids have roughly equivalent physical chemical properties (Table 2). Further these properties follow a general trend with succinic acid (C4) having a lower boiling point, vapor pressure, and Kow, and higher density, melting point, and water solubility than adipic acid (C6). Glutaric acid has physical chemical properties that generally fall within the values for succinic and adipic acids. Thus a true trend for the alkane dicarboxylic acid category exists.

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Density	1.360 at 25°/4°C	1.429 at 15°/4°C	I.564 at 15°/4°C	1.23 at 20°C
Partition Coefficient (log Kow)	0.08 1	-0.29	-0.59	No Data

Ecotoxicity data are essentially equivalent for the category members (Table 3). The environmental fate data indicate all materials are readily biodegradable and do not bioaccumulate. Fugacity model prediction for the alkane dicarboxylic acids indicate these materials will act similarly in regards to partitioning in the environment. Modeled data shows that all 3 test materials are essentially the same in terms of partitioning, with more material partitioning to the soil, and to a slightly lesser extent to water: with virtually none going to air or sediment.

Table 3: Ecotoxicity

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Aquatic toxicity of the alkane dicarboxylic acid category is generally low (Table 4). Acute toxicity to fish for adipic and glutaric acids are similar. Data for succinic acid, although not definitive, indicate that the LC_{50} for succinic acid is in the same general order. This conclusion is also supported by data generated for the mixture of the three dicarboxylic acids. Information with *Duphnia* indicate results for adipic and succinic acids in the same order of magnitude. Finally, acute toxicity to algae indicate that dicarboxylic acids have similar toxicity in these organisms.

Table 4: Aquatic Toxicity

	Adipic Acid	Glutaric Acid	Succinic Acid	Dicarboxylic Acid Mixture
Toxicity to Fish (LC_{50} value)	*97* mg/L (96-hour)	*330* mg/L (24-hour)	>15 ppm (24-hour)	*240-340* mg/L (96-hour)
Toxicity to Invertebrates (EC_{50} value)	*85.7* mg/L (48-hour)	No Data	*374.2* mg/L (48-hour)	>1000 mg/L (48-hour)

Toxicity to Algae (EC_{50} value)	26.6 mg/L (96-hour)	264 mg/L (72-hour)	120 mg/L	35 mg/L (96-hour)

In mammalian species the low toxicity is manifest in high lethal doses in acute studies, limited toxicity (body weight effects) in repeat dose studies, and no effects in teratologic evaluations (Tables 5 and 6). This is not unexpected as succinic acid is a component of carbohydrate metabolism in living systems, and the FDA regulates adipic acid as a GRAS (generally recognized as safe) component. It appears that the LD_{50} may be influenced by chain length as the C4 dicarboxylic acid, succinic acid, has a lower LD_{50} than glutaric (C5) and adipic (C6) acids. A similar relationship also exists in ocular irritation, where severity of response decreases with increasing carbon number. When tested in rabbits, adipic acid produced slight to mild skin irritation, and glutaric and succinic acids produced slight skin irritation. When tested in guinea pigs the mixture produced no to mild skin irritation. In dermal sensitization studies in guinea pigs, adipic acid and the mixture of the acids did not produce skin sensitization.

Table 5: Acute Mammalian Toxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Oral LD_{50} (rat)	5050 mg/kg	2750 mg/kg	2260 mg/kg	6829 mg/kg
Inhalation LC_{50} (rat)	> 7.7 mg/L	No Data	No Data	>0.03 mg/L
Dermal LD_{50} (rabbit)	> 7940 mg/kg	> 10,000 mg/kg	No Data	> 7940 mg/kg
Dermal Irritation	Slight to mild	Slight	Slight	No to mild
Eye Irritation	Mild to moderate	Moderate	Severe	Mild to severe
Dermal Sensitization	Not a sensitizer	No Data	No Data	Not a sensitizer

Repeated exposure studies in rats with adipic acid (2 years), glutaric acid (90 days), and succinic acid (90 days and 2 years, tested as the sodium salt, which is appropriate since on contact with water in living systems it dissociates to the acid form), as well as the mixture of the acids (90 days), have indicated a low degree of toxicity. A low degree of toxicity was also seen in a repeated exposure study (90 days) with glutaric acid in dogs. Concentrations of 1-2% of the individual acids, and 3% of the acid mixture were well

tolerated. Higher concentrations of all 4 test substances were associated with a depressed rate of weight gain. No specific target organ was identified for any of the individual acids or the AGS mixture.

Developmental toxicity studies have been conducted for glutaric and adipic acids in both rat and rabbit (Table 6). These studies resulted in no adverse effects on pregnancy and no embryotoxic or teratogenic effects. It is reasonable to assume that this category does not pose a developmental toxicity hazard.

Evaluation of reproductive toxicity for the alkane dicarboxylic acid category cannot be conducted with currently available data (Table 6). No studies have been conducted to examine the effects of any of these materials on male or female fertility. Histopathological evaluations of the gonads were conducted in some of the repeated dose studies, but were not sufficient to eliminate the possibility of an effect. Based on the similarity of results in acute and repeated dose studies for the alkane dicarboxylic acids, it is anticipated that effects on fertility would be similar. As such it is proposed to evaluate the reproductive effects of adipic acid in an OECD Guideline 422 reproductive toxicity screen.

Table 6: Repeated Dose, Developmental, and Reproductive Toxicity

	Adipic Acid	**Glutaric Acid**	**Succinic Acid**	**Dicarboxylic Acid Mixture**
Repeated Dose Toxicity (NOAEL)	1% in a 2-year study	1-2% in a 90-day study	1.25% in a 90-day study 1% in a 2-year study	3% in a 90-day study
Developmental Toxicity	Not teratogenic	Not teratogenic	No reliable data	No Data
Reproductive Toxicity	No effect on reproductive organs in repeated exposure studies	No effect on reproductive organs in repeated exposure studies	No reliable data	No effect on reproductive organs in a repeated exposure study

Genetic toxicity data are similar between the three acids, supporting a category approach (Table 7). Neither succinic, glutaric, nor adipic acids induce mutations in bacteria, as is the case with the mixture. Similar responses were seen with the 3 diacids and clastogenic activity. Adipic acid was inactive *in vitro* and *in vivo*. Succinic acid was inactive *in vitro;* glutaric was inactive *in vivo*, and essentially inactive *in vitro* (2 assays reported negative results and 1 assay reported positive results). It can be reasonably assumed that succinic acid will be inactive *in vivo* and glutaric inactive *in vitro.* The mixture of the

acids was inactive in point mutations assays in *Salmonella,* unscheduled DNA synthesis (UDS) in rat hepatocytes, and in the HGPRT assay. Somewhat surprisingly, the mixture of the acids was genotoxic in an in *vitro* Chinese hamster ovary (CHO) clastogenicity study. The reason for this response is not known. The mixture was, however, inactive *in vivo.* Taken collectively, it can be concluded that these test substances are inactive for mutagenic and clastogenic effects.

Table 7: Genetic Toxicity

	Adipic Acid	Glutaric Acid	Succinic Acid	Dicarboxylic Acid Mixture
Mutagenic	**No**	**No**	**No**	**No**
Clastogenic	**No**	**No**	**No**	**No**

Overall, the toxicologic database for the individual acids and the mixture is relatively complete, and the information available does not suggest a high level of concern. The database could be enhanced by investigating reproductive toxicity. Table 8 lists the proposed test plan for the dicarboxylic acid category. The shaded cells represent those SIDS endpoints for which testing was recommended.

Table 8: Alkane Diacids Proposed SIDS Test Plan

	Adipic Acid	Glutaric Acid	Succinic Acid	AGS Mixture
Reproductive Assessment	-	-*	-*	

- = No data available.
* = Evaluation of the test substance will be considered based upon the results obtained from the study performed with adipic acid.

Once the reproductive screen on adipic acid is completed the results will indicate if additional testing is needed. If no adverse effects on reproductive function are determined, no additional testing will be conducted. If reproductive function is adversely affected, succinic/glutaric acids will be considered for evaluation to determine if these effects occur across the entire range of alkane dicarboxylic acids.

Exposure Assessment

Dibasic Acid (DBA) is a by-product manufactured in the production of adipic acid at several domestic and regional facilities. Glutaric and succinic acids are non-commercialized by-products of this process. Approximately 94% of the volume of DBA produced is as adipic acid. Approximately 4.25% of the dibasic acid mixture is converted to dibasic esters by esterification of the acid moieties with methanol, either on site or by toll manufacturers. Approximately 1.2% of the DBA production is burned as

fuel at manufacturing sites and the remaining 0.55% is sold to customers or distributors for use as corrosion inhibitors and as a pH buffer for lime and limestone SO_2 scrubbers. All sites that produce and use DBA have safety, health, & environmental practices and procedures in place and utilize engineering controls, environmental controls, and personal protective equipment to manage the risk of exposure above recommended limits. The toll manufactures also have procedures, practices, and controls in place to manage the risk of exposure, and no sites or customers have reported any SHE incidents from the handling of DBA. The major manufacturers of DBA practice Responsible Care@ and assess the ability of potential toll manufacturers and customers to safely handle DBA prior to commencing a commercial relationship. This assessment includes reviews and audits of PPE (personal protective equipment), safety equipment and procedures, structural integrity, and safety practices.

DBAs are primarily the by product of commercial production of adipic acid, an industrial intermediate for the production of Nylon 6,6 for use in fibers, engineering resins, films, and monofiliments. Other applications for adipic acid include flue gas desulphurization, adhesives, and food additives. Adipic acid is generally recognized as safe (GRAS) under 2 1 CFR 184.1009 when used in foods at levels not to exceed current good manufacturing practice in accordance with 2 1 CFR 184. lb 1.

Concerns with adipic acid focus on physical handling of the product. When dispersed as a dust, adipic acid is subject to normal dust explosion hazards. The minimum ignition energy (MIE), a measure of dust explosivity, is 5 mJ. Tests show that unloading 907 kg (2000 lb) bulk bags of adipic acid can generate voltage levels necessary to constitute a spark hazard. The major producers of adipic acid practice Responsible Care@ and follow its distribution management practice.

The sites handling DBA and adipic acid can have from 250 to 2000 personnel (construction, contractor, and plant employees). The area where the substances are manufactured will have from 2 to 5 operators during normal operations and from 10 to 60 people during a shutdown or major construction activity. The DuPont Acceptable Exposure Limit for adipic acid is 5 mg/m^3, 8- and 12-hour TWA. The ACGIH Threshold Limit Value is 5 mg/m^3, 8-hour TWA, and the Workplace Environmental Exposure Level is 5 mg/m^3, 15-minute TWA. OSHA has not established a Permissible Exposure Limit.

Exposure Groups

Data are presented below on various occupational exposures to alkane dicarboxylic acids. As the majority of alkane dicarboxylic acids are produced as site limited intermediates, exposure to these materials are limited. Little exposure to adipic acid, glutaric acid, or succinic acid vapor occurs to manufacturing personnel. Exposure to adipic acid, the one alkane dicarboxylic acid with large commercial applications, during the loading of hopper cars and QA/QC in the process lab, is below exposure standards.

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Personal monitoring of DBA vapor samples were collected on silica gel tubes using a low flow pump. Adipic, glutaric and succinic acids were separated by ion exchange chromatography followed by FID detection.

Adipic acid dust TWA samples are collected gravimetrically using 0.8 micron pore sized mixed cellulose ester (MCE) filters that are matched-weighted to within 50 micrograms. Matched-weight refers to two filters that are matched in weight and loaded into a 37 mm cassette. The top filter collects contaminants and the bottom filter serves as a control. After sampling, both filters are removed and weighed; the difference between weights is the total dust sample weight. LOGAN (Lognormal Analysis) is used for characterizing employee exposure to chemicals. LOGAN predicts exposure for an entire group in a given workplace based on a limited number of samples. LOGAN maintains that employee risk of overexposure is less than 5%.

Occupational Exposure to Dicarboxylic Acid Vapor During Manufacture				
Chemical	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
Adipic Acid	14	0.10	0.02	0.58
Glutaric Acid	14	0.13	0.01	0.21
Succinic Acid	13	0.11	0.01	0.15

Exposure to Adipic Acid Dust During Loading Operations				
People	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
8	25	0.5832	0.01	4.1475
16	14	2.26	co.01	15.28

Exposure to Adipic Acid Dust by QA/QC Technical Personnel				
Chemical	No. of Results	Avg. of TWA (mg/m^3)	Min. of Results (mg/m^3)	Max. of TWA (mg/m^3)
16	3	0.10	co.01	0.20

Appendix A

ROBUST SUMMARY FOR ADIPIC ACID

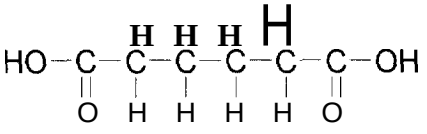
The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as related references in this document.

1.0 Substance Information

CAS Number: 124-04-9

Chemical Name: Hexanedioic acid

Structural Formula:



Other Names:
Adipic acid
1,4-Butanedicarboxylic acid
1,6-Hexanedioic acid
Acifloctin
Acinetten
Adilactetten
Adipate
Adipinic acid
Asapic
Inipol DS
Molten adipic acid

Exposure Limits:
5 mg/m^3, 8- and 12-hour TWA: DuPont Acceptable Exposure Limit (AEL)

5 mg/m^3, 8-hour TWA: ACGIH Threshold Limit Value (TLV)

5 mg/m^3, 15-minute TWA: Workplace Environmental Exposure Level (WEEL; Draft Document 6, May 1992)

2.0 Physical – Chemical Properties

2.1 Melting Point

Value:	152°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown

Reference:	Budavari, S. (ed.) (1996). The Merck Index. An Encyclopedia of Chemicals, Drugs. and Biologicals, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point:

DuPont (1997). Material Safety Data Sheet No. 6053CR.

Ullmann (1974). Enzvklonaedie der Techn. Chemie 7, 106 (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Bayer AG (1990). Safety Data Sheet (08.05.1990) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

FDA (1974). PB-230 305.

Kühne, R. et al. (1995). Chemosphere, 30(11):2061-2077.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 23, John Wiley & Sons, Inc., New York, NY.

Katalog Janssen Chimica (1987/88). (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. Al 7 16 (December 8) (MALLIN/1038).

2.2 Boiling Point

Value :	330.5°C
Decomposition:	Yes
Pressure:	760 mm Hg
Method:	No Data
GLP:	Unknown
Reference:	FDA (1974). PB-230 305, prepared by Informatics, Inc.
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

Bayer AG (1990). Safety Data Sheet (08.05.1990) (cited in BUA Report (1991). BUA Reports 68-70, p. l-33, edited by S. Wirzel, Wissenschaftliche Verslagsgesellschaft (April)).

Budavari, S. (ed.) (1996). The Merck Index. An Encyclonedia of Chemicals, Drugs, and Biologicals, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ.

DuPont (1997). Material Safety Data Sheet No. 6053CR.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 23, John Wiley & Sons, Inc., New York, NY.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. A 17 16 (December 8) (MALLIN/1038).

Ullmann's Encyclopedia of Industrial Chemistry (1985). 5th ed., Vol. Al, pp. 269-278, VCH, Weinheim (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Katalog Janssen Chimica (1987188). (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

2.3 Density

Value:	1.360
Temperature:	25°/4°C
Method:	No Data
GLP:	Unknown
Results:	No additional data.
Reference:	Budavari, S. (ed.) (1996) The Merck Index. An Encyclouedia of Chemicals, Drugs, and Biologicals, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available.

Additional References for Density:

Bayer AG (1990). Safety Data Sheet (08.05.1990) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

DuPont (1997). Material Safety Data Sheet No. 6053CR.

FDA (1974). PB-230 305.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 23, John Wiley & Sons, Inc., New York, NY.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. A 17 16

(December 8) (MALLIN/1038).

Ullmann's Encyclonedia of Industrial Chemistry (1985). 5th ed., Vol. A 1, pp. 269-278, VCH, Weinheim (1985) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

2.4 Vapor Pressure

Value:	3.18×10^{-7} mm Hg
Temperature:	25°C
Decomposition:	No Data
Method:	Extrapolated
GLP:	Unknown
Reference:	Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 2: C5 to C7 Compounds, p. 391, Gulf Publ. Co., Houston, TX (SRC Database).
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure:

BASF AG (1991). Safety Data Sheet, Adipic acid (119 1) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (Feb. 18)).

Danley, D. E. and C. R. Campbell (1978). Kirk-Othmer Encvcl. Chem. Tech., 3rd ed., 1:510-531 (ENVIROFATE/112606).

DuPont (1997). Material Safety Data Sheet No. 6053CR.

Granovskaya, A. (1947). Zh. Fiz. Khim., 21:967 (cited in Kroschwitz, J. I. (ed.) (1991). Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed., p. 46'7, John Wiley and Sons, New York, NY).

Kraft, F. and H. Noerdlinger (1889). Ber. Dtsch. Chem. Ges., 22:818 (cited in Kroschwitz, J. I. (ed.) (199 1). Kirk-Othmer Encyclopedia of Chemical Technology, 4th ed., p. 467, John Wiley and Sons, New York, NY).

Jordan, E. T. (1954). Vapor Pressure of Organic Compounds, Inter-Science Publishers, Inc., New York, NY (ISHOW/306690).

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. A1716 (December 8) (MALLIN/ 103 8).

National Safety Council (1985). Adipic Acid, Data Sheet I-438-Reaf. 85, Chicago, Illinois (cited in WEEL (1992). Workplace Environmental Exposure Level Guide: Adipic Acid, Draft 6 (May)).

Ullmann's Encyclopedia of Industrial Chemistry (1985). 5th ed., Vol. Al, pp. 269-278, VCH, Weinheim (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

2.5 Partition Coefficient (log Kow)

Value:	0.08 l
Temperature:	25°C
Method:	OECD Guideline 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
GLP:	No
Reference:	BASF AG (n.d.). Department of Analytics Unpublished Data (BRU 88.12 1) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).
Reliability:	Not assignable because limited study information was available.

Additional References for Partition Coefficient (log Kow):

BASF AG (n.d.). Department of Analytics Unpublished Data (BRU 88.077) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Bayer AG (1991). Calculation UWS Product Security (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Collander, R. (195 1). Acta Chem. Scand., 5:774-780 (ISHOW/306693).

Hansch, C. and A. J. Leo (1981). Medchem Project, Issue No. 19, Pomona College, Claremont, CA (ENVIROFATE/112590).

Hansch, C. et al. (1995). Exploring QSAR – Hydrophobic, Electronic, and Steric Constants, p. 23, American Chemical Society, Washington, DC (HSDB/188).

Leo, A. J. (1978). Report on the Calculation of Octanol/Water Log P Values for Structures in EPA Files (ISHOW/306692).

THOR Database Pomona 89, MedChem Software 1989. Daylight, Chemical Information Systems, Claremont, CA 9 17 11, USA (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

2.6 Water Solubility

Value:	3.00×10^4 mg/L
Temperature:	30°C
pH/pKa:	No Data

Method:	No Data
GLP:	Unknown
Reference:	Yalkowsky, S. H. and R. M. Dannenfelser (1992). Aquasol Database of Aqueous Solubility, Version 5, PC Version, College of Pharmacy, Univ. of Arizona - Tucson, AZ (HSDB/188).
Reliability:	Not assignable because limited study information was available.

Additional References for Water Solubility:

Bayer AG (1990). Safety Data Sheet (08.05.1990) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

BASF AG (199 1). Safety Data Sheet, Adipic acid (1/9 I) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Budavari, S. (ed.) (1996). The Merck Index - An Encyclonedia of Chemicals, Drugs, and Biologicals, p. 30, Merck and Co., Inc., Whitehouse Station, NJ.

CITI (ed.) (1992). Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, compiled under the supervision of Chemical Products Safety Division, Basic Industries Bureau MITI (October), published by Japan Chemical Industry Ecology-Toxicology & Information Center (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Dean, J. A. (1987). Handbook of Organic Chemistry, p. l-25 1, McGraw-Hill Book Co., New York, NY (HSDB/188).

DuPont (1997). Material Safety Data Sheet No. 6053CR.

FDA (1974). PB-230 305.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. Al 7 16 (December 8) (MALLIN/1038).

Kühne, R. et al. (1995). Chemosphere, 30(11):2061-2077.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 1 3th ed., p. 23, John Wiley & Sons, Inc., New York, NY.

National Safety Council (1985). Adipic Acid, Data Sheet I-438-Reaf. 85, Chicago, Illinois (cited in WEEL (1992). Workplace Environmental Exposure Level Guide: Adinic Acid, Draft 6 (May)).

Stephan, H. and T. Stephen (1963). Solubilities of Inorganic and Organic

Compounds, Vol. I, Binary Systems, Macmillan Co., New York, NY (ISHOW/306691).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 165, Van Nostrand Reinhold Co., New York, NY.

2.7 **Flash Point**

Value:	196°C
Method:	Closed cup
GLP:	Unknown
Reference:	Lewis, R. J. Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 23, John Wiley & Sons, Inc., New York.
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point:

BASF AG (199 1). Safety Data Sheet, Adipic acid (1/9 1) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Bayer AG (1990). Safety Data Sheet (08.05.1990) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

DuPont (1997). Material Safety Data Sheet No. 6053CR.

FDA (1974). PB-230 305.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. A1716 (December 8) (MALLIN/1038).

NFPA (National Fire Protection Association) (199 1). National Fire Protection Guide. Fire Protection Guide on Hazardous Materials, 10th ed., p. 325M-12, National Fire Protection Association, Quincy, MA (HSDB/188).

Ullmann's Encyclopedia of Industrial Chemistry (1985). 5th ed., Vol. Al, pp. 269-278, VCH, Weinheim (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

2.8 **Flammability**

Results:	Minimum explosive dust concentration is reported as 0.0935 oz/ft^3 (35,000 mg/m^3). Static electricity produced

	during a free fall or conveying may serve as an ignition source. Rated as a strong dust explosion hazard.
Method:	No Data
GLP:	Unknown
Reference:	National Safety Council (1985). Adipic Acid, Data Sheet I-43%Reaf. 85, Chicago, Illinois (cited in WEEL (1992). Workplace Environmental Exposure Level Guide: Adipic Acid, Draft 6 (May)).
Reliability:	Not assignable because limited study information was available.

Additional References for Flammability:

BASF AG (199 1). Safety Data Sheet, Adipic acid (1/9 1) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

DuPont (1997). Material Safety Data Sheet No. 6053CR.

FDA (1974). PB-230 305.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. Al7 16 (December 8) (MALLIN/1038).

NFPA (National Fire Protection Association) (1991). National Fire Protection Guide. Fire Protection Guide on Hazardous Materials, 10th ed., p. 325M-12, National Fire Protection Association, Quincy, MA (HSDB/188).

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	Not Applicable
Temperature:	No Data
Direct Photolysis:	Not Applicable
Indirect Photolysis:	Not Applicable
Breakdown Products:	Not Applicable
Method:	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman, 1988), adipic acid, which has an extrapolated vapor pressure of 7.4×10^{-7} mm Hg at 30°C (Yaws, 1994), will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase adipic acid is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals (SRC, n.d.). The rate constant for the vapor-phase reaction of adipic acid with photochemically-produced hydroxyl radicals has been estimated as

	$5.6x10^{-12}$ cm^3/molecule*sec at 25°C (SRC, n.d.) using a structure estimation method (Meylan and Howard, 1993; SRC, n.d.). This corresponds to an atmospheric half-life of about 2.9 days at an atmospheric concentration of $5x10^5$ hydroxyl radicals per cm^3 (Meylan and Howard, 1993; SRC, n.d.).
GLP:	Not Applicable
Reference:	Bidleman, T. F. (1988). Environ. Sci. Technol., 22:361-367 (HSDB/188).
	Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 2: C5 to C7 Compounds, p. 391, Gulf Publ. Co., Houston, TX (HSDB/188).
	Meylan, W. M. and P. H. Howard (1993). Chemosphere, 26:2293-2299 (HSDB/188).
	SRC (Syracuse Research Corporation) (n.d.). (HSDB/188).
Reliability:	Estimated value based on accepted model.

Additional References for Photodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Dorfman, L. M. and G. E. Adams (1973). NSRD-NBS-46 (NTIS COM-73-50623) (ENVIROFATE/112596).

Knoevenagel, K. and R. Himmelreich (1976). Arch. Environ. Contam. Toxicol., 4:324-333 (cited in Verschueren, K. (1983). Handbook of Environmental Data of Organic Chemicals, 2"" ed., p. 165, Van Nostrand Reinhold Co., New York, NY).

3.2 Stability in Water

Concentration:	Not Applicable
Half-life:	Not Applicable
% Hydrolyzed:	Not Applicable
Method:	The Henry's Law constant for adipic acid is estimated as $4.7x\ 1\ 0^{-12}$ atm-m^3/mole (SRC, n.d.) from its extrapolated vapor pressure, $7.4x10^{-7}$ at 30°C (Yaws, 1994), and measured water solubility, $3.0x\ 10^4$ mg/L at 30°C (Yalkowsky and Dannenfelser, 1992). This value indicates that adipic acid is not expected to volatilize from water surfaces (Lyman et al., 1990; SRC, n.d.). Adipic acid's pKas of 4.44 and 5.4 (Serjeant and Dempsey, 1979) indicate that

adipic acid will exist predominately in the ionized form under environmental pHs (SRC, n.d.). Volatilization of the ionized form from water surfaces is not expected to be an important fate process (SRC, n.d.).

Adipic acid is not expected to undergo hydrolysis (SRC, n.d.) in the environment due to the lack of functional groups to hydrolyze (Lyman et al., 1990). The rate constant for the reaction of adipic acid with hydroxyl radicals in aqueous solution at pH 2 to 2.2 has been measured as 2.0×10^{9} L/mol sec (Buxton et al., 1988). This corresponds to a half-life of about 1.1 years (SRC, n.d.) at an average aqueous hydroxyl radical concentration of 1×10^{-17} mol/L (Mill et al., 1980).

GLP: Not Applicable

Reference:

Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 2: C5 to C7 Compounds, p. 39, Gulf Publ. Co., Houston, TX (HSDB/188).

Yalkowsky, S. H. and R. M. Dannenfelser (1992). Aquasol Database of Aqueous Solubility, Version 5, PC Version, College of Pharmacy, Univ. of Ariz. - Tucson, AZ (SRC Database).

Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 15- 1 to 15-29, American Chemical Society, Washington, DC (HSDB/188).

Buxton, G. V. et al. (1988). J. Phys. Chem. Ref. Data, 17:513-882 (HSDB/188).

Mill, T. et al. (1980). Science, 207:886-887 (HSDB/188).

Serjeant, E. P. and B. Dempsey (1979). Ionization Constants of Organic Acids in Aqueous Solution, IUPAC Chemical Data Series No. 23, p. 989, Pergamon Press, New York, NY (HSDB/188).

SRC (Syracuse Research Corporation) (n.d.). (HSDB/188).

Reliability: Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity):

Media:	Air, Water, Soil, Sediments
Distributions:	Air: <0.001%
	Water: 42.4 %
	Soil: 57.5 %
	Sediment: 0.06 %
Adsorption Coefficient:	Not Applicable
Desorption:	Not Applicable
Volatility:	Not Applicable
Method:	Calculated according to Mackay, Level III, Syracuse Research Center Epiwin Version 3.05. Emissions (1000 kg/hr) to air, water, and soil compartments using EPA Model defaults.
	Data Used:
	Molecular Weight: 146.14
	Henry's Law Constant: 4.71×10^{-12} atm-m^3/mole (SRC Database)
	Vapor Pressure: 3.18×10^{-7} mm Hg (Yaws, 1994)
	Log Kow : 0.08 (Hansch and Leo, 1981)
	Soil Koc : 21.48 (Pckocwin program)
GLP:	No
Reference:	Hansch, C. and A. J. Leo (1981). Medchem Project, Issue No. 19, Pomona College, Claremont, CA.
	Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 2: C5 to C7 Compounds, p. 391, Gulf Publ. Co., Houston, TX.
	Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach was developed by Dr. Donald Mackay and co-workers which is detailed in:
	Mackay, D. (199 1). Multimedia Environmental Models: The Fugacity Approach, pp. 67-183, Lewis Publishers, CRC Press.
	Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.
	Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.
Reliability:	Estimated value based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Value: Adipic acid is considered readily biodegradable. In biodegradability screening studies designed to simulate sewage treatment plants, results ranged from 99% DOC removal in I day to 92% theoretical BOD in 14 days. Degradability of adipic acid in surface waters was demonstrated by a 96% DOC reduction after 19 days using a modification of the OECD Ready-Biodegradability Screening Test 301E. Closed bottles studies, at a standard test concentration of 2 mg/L, resulted in a 83% reduction in BODT over a 30 day period.

Coupled Units Test: 99 ± 4 % DOC removal with a working-in time of 1 day.

Zahn-Wellens Test: 100% DOC removal after 4 days.

MITI Test: 96% DOC removal, with a $BODT_{14}$ of 92%.

Sturm Test: 91% CO_2 evolution, with 100% DOC removal after 28 days.

OECD Screening Test: OECD Guideline 301E "Ready Biodegradability: 96% DOC after 19 days.

Closed Bottle Test: 83% $BODT_{30}$.

Breakdown Products: No Data

Method: Coupled Units Test (Janicke, W. (197 1). Water Res., 5:917-931; Huber, W. and K. H. Popp (1974). Tenside Deterg., 11: 195-197; Fischer, W. K. and P. Gerike (1975). Water Res., 9:1137-1 141; Fischer, W. K. et al. (1975). Water Res., 9: 1131-l 135; Gerike, P. et al. (1979). Water Res., in press): The coupled units test is an adaptation of the OECD Confirmatory Test for the application of summary parameters. It works under steady-state conditions, i.e., as a continuous flow system, and to employ an organic base medium, i.e., to maintain nutrient competition at all times as a model for a communal sewage treatment plant. The principle is steady-state organic nutrients. This test was started with a full load (2.5 g/L of dry matter) of sludge from a communal sewage treatment plant. The concentration was ≥ 12 mg C/L. The results are reported as the working-in

time and the mean DOC removal with tolerance limits at a 95% probability level. Only the DOC removal was reported since the COD removal was considered too undependable.

Zahn-Wellens Test (Zahn, R. and H. Wellens (1974). Chemiker. Z., 98:228-232; Umweltbundesamt (1978). OECD Chemicals Testing Programme. Expert Group C "Persistence" (Degradation/Accumulation) Draft Working Papers, March 3 l, 1978): This test represents an industrial sewage plant, i.e., it was designed to evaluate the removability of industrial chemicals released by point discharge through industrial sewage treatment plants into the aqueous environment. The principle was die-away mineral nutrients. The inoculation was l g sludge/L and the concentration was approximately 400 mg C/L. The results are reported as the percentage DOC removal achieved and the time period within which this DOC removal was attained (14 days). Only the DOC removal was reported since the COD removal was considered too undependable.

Swiss EMPA Test (1977): This test is very similar to the Zahn-Wellens test, but is conducted at a different test substance to sludge ratio. The principle is die-away mineral nutrients. The inoculation was 2.0 or 0.2 g sludge/L, and the concentration was approximately 50 mg C/L. The removal results always represent 14-day values.

Japanese MITI Test: The Sapromat was used, basically a BOD determination apparatus with an electrolytic oxygen supply for its conduction. The inoculum was prepared in accordance with the procedure, with the exception that the partial inoculum samples were collected from closer surroundings of the investigating laboratory, rather than from all over Germany. These samples encompassed so many different industries that the final inoculation mixture was believed to be representative of all of Germany. The principle was die-away mineral nutrients. The inoculation was 30 mg sludge/L, and the concentration was approximately 50 mg C/L. Only the DOC removals after 14 days and the corresponding biochemical oxygen demands were reported.

Carbon Dioxide Evolution Test (Sturm, R. N. (1973). J. Amer. Oil Chem. Soc., 50: 159-167): The sturm test is a model for surface water. Besides the conventional carbon dioxide production, the DOC removal was followed as a

further biodegradation measure. It employs a preacclimation procedure (therefore, 2 test durations are given, 28 days without and 42 days including acclimation). The preacclimation was modified in such a way that 20 mg/L of test substance, 20 mg/L of yeast extract, and 10% of sewage treatment plant effluent rather than raw sewage were added to BOD water in order to avoid anaerobic conditions. The principle was die-away mineral nutrients. The inoculation was effluent after acclimation, and the concentration was approximately 10 mg C/L.

OECD Screening Test (Umweltbundesamt (1978). OECD Chemicals Testing Programme. Expert Group C "Persistence" (Degradation/Accumulation) Draft Working Papers, March 3 1, 1978; OECD Environment Directorate (1976). Proposed Method for the Determination of the Biodegradability of Surfactants Used in Synthetic Detergents, Paris): This test is a model for surface water and was adapted to the application of the DOC analysis. The principle is die-away mineral nutrients. It was usually run with a test concentration corresponding to 20 mg C/L, later on with 10 mg C/L. In order to maintain an optimal C:N:P ratio, the ammonium concentration specified in the OECD procedure was tripled. Furthermore, a trace metal and an essential vitamin solution were added in order to optimize test conditions. The results are reported as percentage DOC removal after 19 days.

Closed Bottle Test (Fischer, W. K. et al. (1974). Z. Wasser Abwasser Forsch., 7:99-1 18): This test is a model for surface water. The principle is die-away mineral nutrients. The inoculation was 1 drop of effluent/L, and the concentration was approximately 1 mg C/L. Results are reported as the biochemical oxygen demand as a percentage of the theoretically possible amount (theoretical biochemical oxygen demand, BODT) after 30 days at the standard test concentration of 2 mg/L.

GLP: No

Reference: Gerike, P. and W. K. Fischer (1979). Ecotox. Environ. Saf., 3:159-173.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Biodegradation:

Data from these additional sources support the study results summarized above.

These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Chou, W. L. et al. (1979). Biotechnol. Bioeng. Symp., 8:391-414 (ENVIROFATE/112602).

Dore, M. et al. (1975). Trib. Cebedeau, 28:3-1 1 (ENVIROFATE/112600).

Haltrich, W. G. et al. (1980). Vom Wasser, 54:51-62 (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (Feb. 18)).

Hasegawa, Y. et al. (1982). Can. J. Microbiol., 28:942-944 (ENVIROFATE/112593).

CITI (ed.) (1992). Biodegradation and Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan, compiled under the supervision of Chemical Products Safety Division, Basic Industries Bureau MITI (October), published by Japan Chemical Industry Ecology-Toxicology & Information Center (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

Little, A. D. (1967). Study for MCA (cited in Verschueren, K. (1983). Handbook of Environmental Data of Organic Chemicals, 2"" ed., p. 165, Van Nostrand Reinhold Co., New York, NY).

Malaney, G. W. and R. M. Gerhold (1969). J. Water Pollut. Control Fed., 41:R18-R33.

Matsumoto, H. et al. (1989). Eisei Kagaku, 35(1):86-92.

Meinck, F. et al. (1968). lndustrie-Abwaesser, 4. Aufl. (cited in IUCLID (2000). IULCID Data Sheet "Adipic acid" (Feb. 18)).

Ripin, M. J. et al. (1970). NTIS PB 199365 (ENVIROFATE/112595)

Robinson, D. S. (1964). Antonie Van Leeuwenhoek, J. Microbiol. Serol., 30:303-3 16 (ENVIROFATE/112592).

Tanaka, H. et al. (1977). Hakkokogaku Kaishi, 55:57-61 (ENVIROFATE/112594).

Urano, K. and Z. Kato (1986). J. Hazardous Materials, 13: 147-159 (BIODEG/102342).

U.S. Coast Guard, Department of Transportation (1984-1985). CHRIS - Hazardous Chemical Data, Volume II, U. S. Government Printing Office, Washington, DC (HSDB/188).

Zahn, R. and W. Huber (1975). Tenside Deters., 12:266-270 (ENVIROFATE/112603).

Zahn, R. and H. Wellens (1980). Wasser Abwasser Forschung, 13(1): l-7 (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (Feb. 18)).

3.5 Bioconcentration

Value:	BCF 0.68 (SRC, n.d.). According to a classification scheme (Franke et al., 1994), this BCF value suggests that bioconcentration in aquatic organisms is low (SRC, n.d.).
Method:	The estimated value was calculated using a measured log Kow of 0.08 (Hansch et al., 1995) and a recommended regression-derived equation (Lyman et al., 1990).
GLP:	Not Applicable
References:	Hansch, C. et al. (1995). Exploring QSAR. Hydrophobic, Electronic, and Steric Constants, ACS Prof. Ref. Book, Heller, S. R. (consult. ed.), p. 23, American Chemical Society, Washington, DC (HSDB/188). Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 5-4, 5-10, American Chemical Society, Washington, DC (HSDB/188). Franke, C. et al. (1994). Chemosphere, 29:1501-1504 (HSDB/188). SRC (Syracuse Research Corporation) (n.d.). (HSDB/188).
Reliability:	Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Study No. 1

Type:	**96-hour LC_{50}**
Species:	Fathead minnow *(Pimephales promelas)*
Value:	**97** mg/L
Method:	Juvenile fathead minnows were from 4 to 8 weeks old and varied in length from 1.1 to 3.1 cm. Fish were acclimated in flowing water 1 I cm deep in a holding trough for at least 48 hours before the test was performed. Water temperature was 18-22°C. Test solutions were prepared by adding a weighed amount of the test substance to a 9-L glass carboy

containing 4 L of Lake Superior water. Solution components were thoroughly mixed by shaking, and were then poured into 2 glass battery jars for preparation of test concentrations. All concentrations were nominal; none were analyzed to determine concentration levels. A fiberglass trough of the same dimensions and water depth as used for acclimation served as a water bath for maintaining test solutions at 1822°C.

The static test was conducted in 3-L cylindrical glass battery jars containing 2 L of test water. Ten fish were placed into each battery jar, so that 20 individuals were tested at each concentration. A glass cover was placed over each jar to reduce evaporation. The test waters were not aerated, and fish were not fed during the test. Complete immobilization of the fish was considered the biological endpoint and equated with death. Fish mortality was measured after 1, 24, 48, and 96 hours. Standard graphical procedures were followed for determining concentrations that would result in 50% mortality.

Analyses of the test waters for dissolved oxygen and pH were made at the beginning and 1 or 2 times during the course of the test. Water temperature was measured daily in 2 of the test containers.

GLP: No

Test Substance: Adipic acid, purity reagent grade

Results: The 1-, 24-, 48-, and 72-hour LC_{50}s were > 300, 172, 114, and 97 mg/L, respectively. The pH measured ≤ 5.9 units during the test.

Reference: Mattson, V. R. et al. (1976). Ecol. Res. Ser. EPA-600/3-76-097, Environ. Res. Lab., U. S. EPA, Duluth, MN.

Reliability: Medium because a suboptimal study design was used. Only nominal test concentrations were used.

Study No. 2

Type: **24-hour LC_{50}**

Species: Bluegill sunfish *(Lepomis marochirus)*

Value: <330 mg/L

Method: The methods used were outlined in Freeman, L. (1953). Sewage and Industrial Wastes, 25(7):845. The daily feeding of the fish was discontinued for 24 hours prior to the beginning of the test, and any fish showing signs of being in distress were removed from the tank during this period. The test was conducted in glass jars with a total capacity of 8 L, at 21.5-22.0°C. The test solution was prepared and adjusted

	to temperature in a constant-temperature bath at least 1 hour prior to the beginning of the test. The solution was aerated for at least 10 minutes, or until the dissolved oxygen level reached a minimum of 7-8 ppm. The air stream was then reduced to a rate just sufficient to maintain the dissolved oxygen level. As soon as 10 fish were placed in the test solution, the time was recorded and the fish were carefully observed for signs of anoxia or any other signs of extreme discomfort. After 24 hours, the test solution was checked for the percentage of mortality and the general condition of the surviving fish.
GLP:	No
Test Substance:	Adipic acid, purity not specified
Results:	No additional data.
Reference:	Dowden, B. F. and H. J. Bennett (1965). J. Water Pollut. Control Fed., 37(9):1308-1316.
Reliability:	Low because an inappropriate method or study design was used.

Additional References for Acute Toxicity to Fish:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Bayer AG (n.d.). Unpublished Data (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

BASF AG (1980). Department of Toxicology, Unpublished Investigation (79/557) (12.11.80) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Hutzinger, 0. et al. (1988). Utility of the QSAR Modeling System for Predicting the Toxicity of Substances on EINECS, Preliminary Report to VCI (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Lysak, A. and J. Marcinek (1972). Rocz. Nauk Roln. Ser. H Rybactwo, 94(3):53-63 (AQUIRE/1045689).

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. A171 6 (December 8) (MALLIN/1038).

Verschueren, K. (1996). Handbook of Environmental Data on Organic Chemicals, 3rd ed., p. 138, Van Nostrand Reinhold Co., New York, NY (HSDB/188).

4.2 Acute Toxicity to Invertebrates

Type:	**24- and 48-hour EC_{50}**
Species:	*Daphnia magna*
Value:	**85.7** mg/L
Method:	EG-Richtlinie 79/83 1/EWG, C.2 "Acute Toxicity for *Daphnia"*
GLP:	Unknown
Test Substance:	Adipic acid, purity not specified
Results:	The 24- and 48-hour EC_0 was 62.5 mg/L, and the 24- and 48-hour EC_{100} was 125 mg/L.
Reference:	BASF AG (1988). Unpublished Investigation of 28.01.1988 (l/l 136/2/87) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (February 18)).
Reliability:	Medium because a suboptimal study design was used and limited study information was available.

Additional References for Acute Toxicity to Invertebrates:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

BASF AG (1988). Ecology Laboratory: Unpublished Investigation of 28.01.1988 (l/l 136/2/87) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Rhone Poulenc (1983). Unpublished Data (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

4.3 Acute Toxicity to Aquatic Plants

Type:	**96-hour EC_{50}**
Species:	*Scenedesmus subspicatus*
Value:	**26.6** mg/L
Method:	Algentest in Anlehnung an UBA (algae test following UBA)
GLP:	Unknown
Test Substance:	Adipic acid, purity not specified
Results:	The low pH value with higher adipic acid concentrations might be jointly responsible for the toxicity development in the alga test. The EC_{20} was 13.6 mg/L, and the EC_{100} was **56.9** mg/L.
Reference:	BASF AG (1988). Unpublished Investigation of 15.1.1988 (l/l 136/87/t96) (cited in IUCLID (2000). IUCLID Data Sheet, "Adipic acid" (February 18)).

Reliability: Medium because a suboptimal study design was used and limited study information was available.

Additional References for Acute Toxicity to Aquatic Plants:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

BASF AG (1988). Unpublished Investigation of 14.01.1988 (2/1 136/87/t72) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

BASF AG (1988). Ecology Laboratory: Unpublished Investigation of 15.1.1988 (2/1 136/87/t96) (cited in IUCLID (2000). IUCLJD Data Sheet "Adipic acid" (February 18)).

Meinck, F. et al. (1968). Industrie-Abwaesser, 4. Aufl. (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Study No. 1

Type:	**Oral LD_{50}**
Species/Strain:	Male and female rats/Sprague-Dawley
Value:	5050 mg/kg
Method:	OECD 40 1, except used smaller number of animals (5/group). Calculations were according to the method of deBeer, 1945.
GLP:	No
Test Substance:	Adipic acid (tested as a 20% solution in corn oil), purity not specified
Results:	Mortality ratios of 0/5, 2/5, 3/5, and 5/5 occurred at 3 160, 3980, 5010, and 63 10 mg/kg. All deaths occurred in l-3 days. Toxic signs included reduced appetite and activity. Necropsy findings on decedents included hemorrhagic lungs, discolored livers, and acute g.i. inflammation. The survivors had normal viscera on necropsy.
Reference:	Solutia Inc. (1975). Unpublished Data, YO-75- 187. deBeer, E. J. (1945). J. Pharmacol. Experimen. Ther., 85:1.
Reliability:	High because a scientifically defensible or guideline method was used.

Study No. 2

Type:	**Oral LD_{50}**
Species/Strain:	Male mice/Strain not specified
Value:	1900 mg/kg (limits of error, 1640-2200 mg/kg)
Method:	A 3.0% aqueous solution of adipic acid, kept at body temperature, was tried, but proved impractical at sufficiently large doses to determine an LD_{50}. Therefore, a 6.0% suspension of adipic acid in 0.5% methylcellulose was administered to 13 mice/dose at doses of 1500, 2000, or 2500 mg/kg. An autopsy was performed on animals that died, and survivors were sacrificed at 10 days.
GLP:	No
Test Substance:	Adipic acid, purity not specified
Results:	At 1500, 2000, and 2500 mg/kg mortality of the animals was 3/13, 8/13, and 9/13, respectively. Autopsies of the mice that died showed marked distention of the stomach and small intestine, with a spastic contraction of the cecum. There was also evidence of irritation and hemorrhage of the intestines. Initial mortality developed overnight and incidence continued throughout the first week, after which survivors appeared normal.
Reference:	Horn, H. J. et al. (1957). J. Agric. Food Chem., 5(10):759-762. Hazleton Laboratories (1950). Unpublished Data (January 2).
Reliability:	Medium because a suboptimal study design was used.

Additional References for Acute Oral Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Anon. (1983). Gig. Sanit., 48:72, originally cited in Registry of Toxic Effects of Chemical Substances, NIOSH ed., 1991 (cited in Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 4th ed., Volume II, p. 3574, John Wiley and Sons, Inc., New York, NY).

BASF (1978). BASF Data, "Bericht ueber die Pruefung der akuten oralen Toxizitaet von Adipinsaeure an der Ratte" (March 28) (cited in IUCLID (2000. IUCLID Data Sheet "Adipic acid" (February 18)).

BASF AG (1978). Department of Toxicology, Unpublished Investigation (XXVI/413) (11 .01.78) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Enders, A. (1941). Arch. Exptl. Path. Pharmakol., 197:706-709 (cited in FDA (1974). PB-230 305, prepared by Informatics, Inc.; and cited in FDA (1976). Contract No. 223-75-2004, prepared by The Life Sciences Research Office).

FDA (1974). PB-245 466, prepared by Litton Bionetics, Incorporated.

Information Profiles on Potential Occupational Hazards: Adipic Acid, Center for Chemical Hazard Assessment, Syracuse Research Corp., Syracuse, NY, Report No. SRC TR 8 l-5 19, NIOSH Contract No. 2 1 o-79-0030 (March 198 1) (cited in National Safety Council (1985). Adipic Acid, Data Sheet I-438-Reaf. 85, Chicago, Illinois (cited in WEEL (1992). Workplace Environmental Exposure Level Guide: Adipic Acid, Draft 6 (May)).

Krapotkina, M. A. et al. (1981). Gig. Truda Prof. Zabolevaniia, 5:46-47 (HSDB/188).

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. A171 6 (December 8) (MALLIN/1038).

Marhold, J. V. (1972). Sbor. Vys. Tox. Vvset. Latek A. Prip., 5 1 (RTECS/AU8400000).

Novikov, Y. V. (1983). Gig. Sanit., 9:72-75 (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Type:	**Inhalation LC_{50}**
Species/Strain:	Rat/Strain not specified
Exposure Time:	4 hours
Value:	> 7.7 mg/L
Method:	No Data
GLP:	Unknown
Test Substance:	Adipic acid, purity not specified
Results:	The l-hour LC_{50}, calculated according to Haber's rule, was > 3 l mg/L.
Reference:	BASF (198 1). Data, Akute Inhalationstoxizitaet LC_{50} an der Ratte, Staub-Aerosol-Versuch (July 3 1) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).
Reliability:	Medium because a suboptimal study design was used.

Additional References for Acute Inhalation Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

BASF AG (1978). Department of Toxicology, Unpublished Investigation (XXVI/413) (11.01.78) [cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Moscato, G. et al. (1984). Clinical Allerav, 14:355-361.

Type:	**Dermal LD_{50}**
Species/Strain:	Male and female rabbits/New Zealand White
Exposure Time:	24 hours
Value:	> 7940 mg/kg
Method:	Minimum lethal dose was determined using l-2 rabbits per group. A 24-hour dermal exposure under occluded conditions was conducted. Necropsy was conducted after a 14-day observation period.
GLP:	No
Test Substance:	Adipic acid (tested as a 40% solution in corn oil), purity not specified
Results:	No deaths occurred at 5010 mg/kg (0/1) or 7940 mg/kg (012). Observations included reduced appetite and activity. The viscera were normal at necropsy.
Reference:	Solutia Inc. (1975). Unpublished Data, YO-75-187.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Dermal Toxicity: None Found

Type:	**Dermal Irritation**
Species/Strain:	Rabbits/Albino
Method:	Six male albino rabbits were clipped free of hair on the trunk and lateral areas, and placed in FDA-type stocks. Doses of 0.5 g of 50% (wt./wt.) paste of the test material in propylene glycol were applied to the intact skin under gauze squares. Rubber sheeting was then loosely wrapped around the trunk and secured with adhesive tape. After 24 hours, the rabbits were removed from the stocks, the patches were taken off, and the reactions were observed. Observations were also made at 48 hours and scored according to the system of the regulations of the Federal Hazardous Substances Act described in the Federal Register, Section 1500.41 (1973).
GLP:	No
Test Substance:	Adipic acid, 99.99% purity
Results:	Adipic acid produced very slight to mild skin irritation on 3/6 rabbits tested. According to the Federal Hazardous Substances Act, the material is not considered a primary irritant, but upon repeated contact may be mildly irritating.
Reference:	DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 334-74.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Solutia Inc. (1975). Unpublished Data, YO-75-187.

BASF (1978). Data, "Bericht ueber die Pruefung der primaeren Hautreizwirkung von Adipinsaeure an der Reuckenhaut weisser Kaninchen" (March 28) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

BASF (1978). Data, "Bericht ueber die Pruefung auf primaere Reizwirkung von Adipinsaeure am Auge weisser Kaninchen" (March 28) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

BASF AG (1978). Department of Toxicology, Unpublished Investigation (XXVI/4 13) (11 .O 1.78) (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Novikov, Y. V. (1983). Gig. Sanit., 9:72-75 (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Data from this additional source were not summarized because the focus of the study was skin corrosion potential.

DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 190-74.

Type: **Dermal Sensitization**
Species/Strain: Guinea pigs/Albino
Method: A test for primary irritation was conducted by applying, and lightly rubbing in, approximately 0.05 mL of a 50% and 25% suspension (wt./wt.) of the test material in propylene glycol (PG) on the shaved intact shoulder skin of 10 male guinea pigs. To test for the sensitization potential, a series of 4 sacral intradermal injections was given, 1 each week over a 3-week period, which consisted of 0.1 mL of a 1 .O% solution (wt./vol.) of the test material in water. Following a 2-week rest period, the test animals were challenged for sensitization by applying, and lightly rubbing in, approximately 0.05 mL of a 50% and 25% suspension (wt./vol.) of the test material in PG on the shaved intact shoulder skin. A group of IO previously unexposed guinea pigs received similar

	applications at the time of challenge to provide direct comparison of the challenge reactions on skin of similar age.
GLP:	No
Test Substance:	Adipic acid, approximately 100% purity
Results:	Adipic acid produced very mild to no skin irritation when tested on the shaved intact skin of male albino guinea pigs at a concentration up to 50% in propylene glycol. It did not cause skin sensitization.
Reference:	DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 569-74.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for Dermal Sensitization:

Data from this source were not summarized because the result was inconsistent with the study summarized above and the study design was not adequate. Delayed cutaneous hypersensitivity to a patch test with adipic acid was reported in a laboratory worker in a factory producing polyester resins.

Malten, K. E. and R. L. Zielhuis (1964). Industrial Toxicology and Dermatology in the Production and Processing of Plastics, Elsevier Monographs, Amsterdam (cited in National Safety Council (1985). Adipic Acid, Data Sheet I-438-Reaf. 85, Chicago, Illinois (cited in WEEL (1992). Workplace Environmental Exposure Level Guide: Adipic Acid, Draft 6 (May)).

Type:	**Eye Irritation**
Species/Strain:	Rabbits/Albino
Method:	Ten mg of the test material was placed into the right conjunctival sac of each of 2 albino rabbits. Twenty seconds after contact, 1 treated eye was washed with tap water for 1 minute. The treated eye of the other rabbit was not washed. Observations of the cornea, iris, and conjunctiva were made at 1 and 4 hours, and at 1, 2, 3, 7, and 14 days. A biomicroscope and fluorescein stain were used at examinations after the day of treatment. In a 2nd procedure, 0.1 mL (57.1 mg) of the lightly compacted powder was placed into the right conjunctival sac of each of 2 albino rabbits. After 20 seconds, 1 treated eye was washed with tap water for 1 minute. The treated eye of the other rabbit was not washed. Observations of the cornea, iris, and conjunctiva were made at 1 and 4 hours, and at 1, 2, 3, and 7 days. A biomicroscope and fluorescein stain were used at examinations after the day of treatment.
GLP:	No

Test Substance:	Adipic acid, purity 99.99%
Results:	Ten mg of adipic acid produced no cornea1 and a minimal iritic effect with a mild conjunctival irritation. At 7 days, there was a minimal conjunctival irritation, and the eye was normal within 14 days. An eye dosed with 10 mg of the compound and promptly washed had mild conjunctival irritation with no cornea1 or iritic effect, and was normal within 3 days. Adipic acid (57.1 mg of powder) produced mild opacity of the cornea with minimal iritic effect and moderate to mild conjunctival irritation. The eye was normal at 7 days. An eye dosed with 57.1 mg of the compound and promptly washed produced a transient, mild opacity with no iritic effect, and a moderate to mild conjunctival irritation. The eye was normal within 3 days.
Reference:	DuPont Co. (1974). Unpublished Data, Haskell Laboratory Report No. 333-74.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Eye Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Solutia Inc. (1975). Unpublished Data, YO-75-187.

BASF (1978). Data, Bericht ueber die Pruefung der akuten Haut- und Schleimhautreizwirkung von Adipinsaeure am Auge weisser Kaninchen (March 28) (cited in IUCLID (2000). IUCLID Data Sheet “Adipic acid” (February 18)).

BASF (1978). Data, Bericht uber die Pruefung auf primaere Reizwirkung von Adipinsaeure am Auge weisser Kaninchen (March 28) (cited in IUCLID (2000). IUCLID Data Sheet “Adipic acid” (February 18).

BASF AG (1978). Department of Toxicology, Unpublished Investigation (XXVI/413) (11 .01.78) (cited in IUCLID (2000). IUCLID Data Sheet “Adipic acid” (February 18)).

Krapotkina, M. A. et al. (1981). Gig. Truda Prof. Zabolevaniia. 5:46-47 (HSDB/188).

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. A1716 (December 8) (MALLIN/1038).

Marhold, J. V. (1986). Prehled Prumvslove Toxikologie, Organicke Latky, Prague, Czechoslovakia, Avicenum (RTECS/AU8400000).

Novikov, Y. V. (1983). Gig. Sanit., 9:72-75 (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Data from this additional source were not summarized because the result was inconsistent with the majority of the other findings.

Mallinckrodt, Inc. (1986). Adipic Acid Material Safety Data Sheer (MSDS), Mallinckrodt, Inc., Science Products Division, P.O. Box M, Paris, Kentucky (December) (cited in National Safety Council (1985). Adipic Acid, Data Sheet I-438-Reaf. 85, Chicago, Illinois (cited in WEEL (1992). Workplace Environmental Exposure Level Guide: Adipic Acid, Draft 6 (May)).

5.2 Repeated Dose Toxicity

Study No. 1

Type:	**2-Year Chronic Feeding Study**
Species/Strain:	Rats/Carworth Farms
Sex/Number:	Male and female/20 per exposure level (males); 10 control females and 19 test females
Exposure Period:	2 years
Frequency of Treatment:	*Ad libitum*
Exposure Levels:	Males: 0, 0.1, 1.0, 3.0, 5.0% Females: 0, 1.0%
Method:	Rats were fed either the basal laboratory diet, or the basal diet to which adipic acid was added. Body weights, food consumption, and general appearance were recorded weekly throughout the experimental period. Whenever possible, animals that died were examined, and gross pathology was performed. After 2 years, surviving rats were weighed, killed, and examined grossly. Ten organ weights were recorded for approximately ½ of each group of males, and 4 organ weights were recorded for females. Microscopic examination of 15 tissues was done on a representative number of animals from each group.
GLP:	No
Test Substance:	Adipic acid, purity not specified
Results:	Males: The percent survival for each test group was better than for the control group. There were no body weight differences throughout the 2-year period in rats treated with 0.1 or 1 .O% adipic acid. During the rapid growth period, the weight gains of the 3.0 and 5.0% adipic acid groups were

significantly less than the control groups, Throughout the latter half of the study, the average body weights were not remarkable, although the 5.0% dose group was consistently the lowest. There was a slight, but consistent, reduction in food consumption at 5.0%. Throughout the study, the following clinical signs were observed among all groups, including controls: wheezing, blood-tinged crust about the noses and eyes, and body sores. The incidence of these findings did not appear to be significantly different among the groups although a lower incidence of signs indicative of respiratory infection and body sores occurred in the 5.0% adipic acid group. The incidence of lung pathology and tumor growth appeared to be equally distributed among all groups, including the controls. When the surviving males were sacrificed at the end of the 2-year period, there was no significant gross pathology that was test substance-related. Soft edematous testes were noted at least as frequently in the controls as in the experimental animals. There was no significant difference in organ weights or microscopic examination.

Females: There were no significant differences in body weight gains or food consumption. Clinical signs noted in control and test groups included blood-tinged crust about the eyes and noses, unthriftiness, and body sores. There were no significant differences in organ weights, gross, or microscopic pathology.

Reference: Horn, H. J. et al. (1957). J. Agric. Food Chem., 5(10):759-762.

Hazleton Laboratories (1952). Unpublished Data (August 20).

Reliability: High because a scientifically defensible or guideline method was used.

Study No. 2

Type:	**Subacute Inhalation**
Species/Strain:	Rats
Sex/Number:	Male and Female/2 per sex
Exposure Period:	15 exposures
Frequency of Treatment:	6-hours/day
Exposure Levels:	126 µg/L
Method:	Rats were exposed to adipic acid through a powdered solid injected into a metered air stream at a known rate. Animals were maintained in the exposure chamber for 6 hours, and

	between repeated daily exposures, they were returned to their cages where food and water were freely available. The rats were weighed each morning, and their conditions and behavior were recorded throughout the exposure period. Urine was collected overnight after the last exposure day for biochemical tests, where 5 urine parameters were recorded. On the following day, the rats were sacrificed, and 10 hematological parameters were observed. A gross examination was performed, and 5-9 tissues were saved for microscopic examination.
GLP:	No
Test Substance:	Adipic acid, purity not specified
Results:	Adipic acid produced no toxic signs. Blood tests were normal, and organs appeared normal upon gross examination.
Reference:	Gage, J. C. (1970). Brit. J. Industr. Med., 27: l-l 8.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Repeated Dose Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Cummings, C. E. and J. Roseman (1985). Health Hazard Evaluation Report No. HETA-83-166-1594, Witco Chemical Corporation, Perth Amboy, New Jersey (cited in TNO BIBRA International Ltd. (1991). Toxicity Profile: Adipic acid and its sodium salts).

DuPont Co. (1943). Unpublished Data, Haskell Laboratory Report No. 14-43.

Enders, A. (1941). Arch. Exptl.Path. Pharmakol., 197:706-709 (cited in FDA (1974). PB-230 305, prepared by Informatics, Inc.).

FDA (1974). PB-245 466, prepared by Litton Bionetics, Incorporated.

Hazleton Laboratories (1950). Unpublished Data (March 14).

Lang, K. and A. R. Bartsch (1953). Biochem. Ztschr., 323:462-468 (cited in FDA (1974). PB-230 305, prepared by Informatics, Inc.).

Moody, D. E. and J. K. Reddy (1978). Toxicol. Aopl. Pharmacol., 45:497-504.

NAS/NRC (1943). The toxicity of adipic acid. Adipic acid, 7-safety information (cited in FDA (1974). PB-230 305, prepared by Informatics, Inc.).

Weitzel, G. (1947). Hoppe-Seyler's Z. Physiol. Chem., 282: 185, originally cited in JECFA (1967). 9th and 10" Reports of the Joint FAO/WHO Expert Committee on Food Additives, WHO Fd Add. Ser. No. 40A, B, C, and NIOSH (1981). Information Profiles on Potential Occupational Hazards: Adipic Acid, Report No. SRC TR 8 1-5 19, Contract No. 2 1 o-79-0030, National Institute for Occupational Safety and Health, Rockville, MD (cited in TNO BIBRA International Ltd. (199 1). Toxicity Profile: Adipic acid and its sodium salts).

5.3 Developmental Toxicity

Study No. 1

Species/Strain:	Rats/Wistar
Sex/Number:	Female/25, 25, 25, 25, 24 in the 0, 2.9, 13, 62, and 288 mg/kg groups, respectively
Route of Administration:	Gavage
Exposure Period:	Days 6- 15 of Gestation; Cesarean section Day 20
Frequency of Treatment:	Daily
Exposure Levels:	0, 2.9, 13, 62,288 mg/kg
Method:	Virgin adult females were mated with young adult males, and observation of a vaginal sperm plug was considered Day 0 of gestation. Females were dosed by gavage from gestation days 6- 15. Body weights were recorded, and all animals were observed daily for appearance and behavior with particular attention to food consumption and weight. On Day 20 all dams were subjected to cesarean section, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The urogenital tract of each female was examined in detail for gross anatomical normality. The body weights of the live pups were recorded, and all fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations. The remaining 2/3 were examined for skeletal defects.
GLP:	No
Test Substance:	Adipic acid, purity not specified
Results:	The administration of up to 288 mg/kg of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. A summary of other reproductive outcomes (represented as means/litter, except for resorptions and live litters) are provided in the table below:

Dose (mg/kg):	0	2.9	13	62	288
Corpora Lutea:	11.7	12.6	12.1	11.2	11.4
Implantations:	11.4	11.3	10.6	11.1	11.5
Total No. of Resorptions:	2	6	3	0	7
Total No. of Fetuses:	11.2	11.0	10.3	11.1	11.2
Total No. of Live Litters:	20	23	24	22	20
Mean Fetal Weight (g):	3.88	3.89	3.83	4.01	3.99

Reference: U. S. Food and Drug Administration (1972). Food and Drug Laboratories, Inc. Report PB-22 1 802 (February 26).

Reliability: High because a scientifically defensible or guideline method was used.

Study No. 2

Species/Strain: Rabbits/ Dutch-belted

Sex/Number: Female/19, 13, 16, 15, 20 in the 0, 2.5, 12, 54, and 250 mg/kg groups, respectively

Route of Administration: Gavage

Exposure Period: Days 6- 18 of Gestation; Cesarean section Day 29

Frequency of Treatment: Daily

Exposure Levels: 0, 2.5, 12, 54,250 mg/kg

Method: On Day 0, each doe was given an injection of human chorionic gonadotropin, and was artificially inseminated 3 hours later. Females were dosed by gavage from gestation days 6-l 8. Body weights were recorded, and all animals were observed daily for appearance and behavior with particular attention to food consumption and weight. On Day 29 all does were subjected to cesarean section, and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The urogenital tract of each female was examined in detail for gross anatomical normality. The body weights of the live pups were recorded, and all fetuses were examined grossly for the presence of external congenital abnormalities. The live fetuses of each litter were placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were then sacrificed, and examined for visceral abnormalities. In addition, all fetuses were examined for

skeletal defects.

GLP: No

Test Substance: Adipic acid, purity not specified

Results: The administration of up to 250 mg/kg of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation, or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. A summary of other reproductive outcomes (represented as means/litter, except for resorptions and live litters) are provided in the table below:

Dose (mg/kg):	0	2.5	12	54	250
Corpora Lutea:	9.45	10.8	9.82	11.9	10.1
Implantations:	7.00	9.00	8.60	8.80	7.29
Total No. of Resorptions:	10	9	14	13	16
Total No. of Fetuses:	6.09	7.30	6.70	6.50	5.57
Total No. of Live Litters:	11	9	9	8	12
Mean Fetal Weight (g):	42.3	38.1	40.0	39.4	41.4

Reference: U. S. Food and Drug Administration (1974). Food and Drug Laboratories, Inc. Report PB-267 202 (February 26).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Developmental Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

U. S. Food and Drug Administration (1972). Food and Drug Laboratories, Inc. Report PB-22 1 802 (February 26).

Verrett, M. J. (1974). Investigation of the toxic and teratonenic effects of GRAS substances in the developing chick embryo: Adipic acid. Food and Drug Administration, Department of Health, Education, and Welfare, Washington, DC (cited in Food and Drug Administration (1976). SCOGS-80, Contract No. FDA 223-75-2004, prepared by The Life Sciences Research Office).

5.4 Reproductive Toxicity: No Data.

Additional Reference for Reproductive Toxicity:

Data from this source were not summarized because the study design was not adequate.

Lang, K. and A. R. Bartsch (1953). Biochem. Ztschr., 323:462-468 (cited in FDA (1974). PB-230 305, prepared by Informatics, Inc.).

5.5 Genetic Toxicity

Type:	***In* vitro Bacterial Reverse Mutation Assay**
Tester Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538 and *Escherichia coli* strain WP2
Exogenous Metabolic Activation:	With and without Aroclor®-induced rat liver S-9
Exposure Concentrations:	0, 0.033, 0.10, 0.33, 3.3, and 10 mg/plate
Method:	The standard *S. typhimurium* plate-incorporation assay was performed as described by Ames et al. (1975). Mutat. Res., 31:347-364. The *E. coli* test was performed by the same procedure as the *S. typhimurium* plate-incorporation assay except that each liter of base agar was supplemented with 10 mL (1% v/v) of Oxoid nutrient broth (CM67) to provide a trace of tryptophan. All platings were performed in duplicate and all tests were repeated. Concurrent positive controls were run with each test, both with direct-acting mutagens and with mutagens requiring S-9 activation.
GLP:	Unknown
Test Substance:	Adipic acid, purity not specified
Results:	Negative
Remarks:	Adipic acid gave no evidence of inducing increased revertant counts in any of the bacterial strains used. The positive control substances produced the expected mutagenic responses.
Reference:	Prival, M. J. et al. (1991). Mutat. Res., 260:321-329.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for In *vitro* Bacterial Reverse Mutation Assay:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Solutia Inc. (1978). Unpublished Data, SR-85X-20, FDA contract, SRI Project No. LSU-6909.

Solutia Inc. (1978). Unpublished Data, SR-85-x020.

FDA (1974). PB-245 466, prepared by Litton Bionetics, Incorporated (December 9).

Shimizu, H. et al. (1985). Jpn. J. Ind. Health, 27:400-419 (cited in IUCLID (2000). IUCLID Data Sheet "Adipic acid" (February 18)).

Simmon, V. F. and S. L. Eckford (1978-1979). SRI International, Project Report LSU-6909 (cited in Brusick, D. J. et al. (1980). Mutat. Res., 76: 169-190).

Data from this additional source were not summarized because the study design was not adequate.

Kuroda, M. et al. (1985). Agric. Biol. Chem., 49(6):1893-1895.

Type:	***In vitro* Cytogenetic Study in Anaphase Cells**
Cell Type:	Human embryonic lung cell cultures (WI-38)
Exogenous Metabolic Activation:	Without metabolic activation
Exposure Concentrations:	0, 2, 20, 200 μg/mL
Method:	Cells were suspended in tissue culture medium and planted in milk dilution bottles. The test substance was added at 3 dose levels, using 3 bottles for each level, 24 hours after planting. A preliminary determination of tissue culture toxicity was performed. Cells were incubated at 37°C and examined twice daily to determine when an adequate number of mitoses were present. Cells were harvested by shaking when sufficient mitoses were observed, usually 24-48 hours after planting. The specimens were centrifuged, decanted, and suspended in acetic acid-orecin stain, and placed on a slide, had a coverglass applied, and were fixed. Slides were examined by microscope. Cells in anaphase were observed for non-disjunction as indicative of cytogenetic damage. Analyzed aberrations included bridges, pseudochiasmata, multipolar cells, and acentric fragments. The positive control was triethylene melamine (TEM) and the negative control was saline.
GLP:	No
Test Substance:	Adipic acid, purity not specified

Results:	Negative
Remarks:	No degree of non-disjunction was observed.
Reference:	FDA (1974). PB-245 466, prepared by Litton Bionetics, Incorporated (December 9).
Reliability:	Medium because a suboptimal study design was used.

Additional References for *In* vitro Clastogenicity Studies:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Casto, B. C. and G. G. Hatch (1977). Progress Report NIH-NCI-NOl-CP-45615, pp. l-24 (cited in Heidelberger, C. et al. (1983). Mutat. Res., 114:283-385).

Casto, B. C. and G. G. Hatch (1978). Progress Report NIH-NCI-NOl-CP-45615, pp. 62-75 (cited in Heidelberger, C. et al. (1983). Mutat. Res., 114:283-385).

Type:	***In vivo* Rat Cytogenetie Chromosomal Aberration Assay**
Species/Strain:	Rat/Sprague-Dawley CD
Sex/Number:	Male/l5 per dose group for the acute study (9 negative controls and 5 positive controls); 5 per dose group for the subacute study (3 negative controls)
Route of Administration:	Gavage
Concentrations:	Acute Test I: 0, 3.75, 37.5, 375 mg/kg Subacute Test I: 0, 3.75, 37.5, 375 mg/kg Acute Test II: 0, 5000 mg/kg Subacute Test II: 0, 2500 mg/kg
Method:	In the acute tests, animals were given a single dose of the test substance and killed 6, 24, or 48 hours after administration. For the subacute tests, animals were given 5 doses 24 hours apart and killed 6 hours after the last dose. Four hours after the last test substance administration (2 hours prior to killing) each animal was given 4 mg/kg of colcemid intraperitoneally in order to arrest the bone marrow cells in C-mitosis. Animals were killed, and the bone marrow from 1 femur per animal was collected and processed. Slides were prepared, stained, and examined using microscopes with brightfield optics and xenon light sources. The specimens were scanned with 10X and 24X objectives and suitable metaphase spreads that were countable were examined critically using 40X, 63X, or 100X oil immersion flatfield apochromatic objectives. The chromosomes of each cell were counted and only 50 diploid metaphase spreads per animal were analyzed for

	chromosomal aberrations. Mitotic indices were obtained by counting at least 500 cells. Positive controls in the acute study consisted of animals, which had been given triethylene melamine (TEM), and negative controls for the acute and subacute tests consisted of saline, the vehicle in which the test substance was administered.
GLP:	No
Test Substance:	Adipic acid, purity not specified
Results:	Negative
Remarks:	In the acute test I, neither the variety nor the number of aberrations differed significantly from the negative controls. The expected severe chromosomal damage was observed in the positive control group. The mitotic indices were within normal limits. In the subacute test I, the 37.5 mg/kg level contained 1 cell with a reunion and 1 cell that was polyploid, and the 375 mg/kg level contained 3 cells with breaks and l fragment. These were considered to be within normal limits of historical controls. The negative control group and the 3.75 mg/kg group contained no aberrations. In the acute and subacute test II, neither the variety nor the number of aberrations differed significantly from negative controls; hence, adipic acid was considered non-mutagenic.
Reference:	FDA (1974). PB-245 466, prepared by Litton Bionetics, Incorporated (December 9).
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	**Dominant Lethal Assay**
Species/Strain:	Rats/Sprague-Dawley CD
Sex/Number:	Male rats/10 rats per group
Route of Administration:	Gavage
Concentrations:	Acute Test I: 0, 3.75, 37.5, 375 mg/kg Subacute Test I: 0, 3.75, 37.5, 375 mg/kg Acute Test II: 0, 5000 mg/kg Subacute Test II: 0, 2500 mg/kg
Method:	Rats were administered the test substance by gavage in both the acute study (1 dose) and the subacute study (1 dose per day for 5 days). Following treatment, the males were sequentially mated to 2 females per week for 8 weeks (7 weeks in the subacute study). Two virgin female rats were housed with a male for 5 days (Monday through Friday). These 2 females were removed and housed in a

	cage until killed. The male was rested on Saturday and Sunday, and 2 new females were introduced to the cage on Monday. Females were killed 14 days after separating from the male, and at necropsy the uterus was examined for deciduomata (early deaths), late fetal deaths, and total implantations. The fertility index, preimplantation loss, and lethal effects on the embryos were determined. Positive controls were administered triethylene melamine (TEM), and negative controls were administered saline, the vehicle in which the test substance was administered.
GLP:	No
Test Substance:	Adipic acid, purity not specified
Results:	Negative
Remarks:	In the acute test 1, significant decreases in average implantations at weeks 1 and 4, and corpora lutea at weeks 4 and 7 were observed in the 37.5 mg/kg dose level. Significant increases in preimplantation losses were shown at week 1 for both the 3.75 and 37.5 mg/kg dose groups. In the subacute test I, significant differences between the negative control and experimental groups were shown in a few instances, but no strong indications of change were observed. In the acute test II and subacute test II, the values calculated for fertility index, preimplantation loss, and lethal effects on the embryos did not differ significantly from those obtained from the negative controls; whereas the positive control substance caused a significant preimplantation loss and embryo resorption during the 1st 5 weeks. Comparing these data with the previously obtained values for dose levels of 375, 37.5, and 3.75 mg/kg revealed no dose-response or time-trend patterns, thus indicating that adipic acid does not induce dominant lethal mutations.
Reference:	FDA (1974). PB-245 466, prepared by Litton Bionetics, Incorporated (December 9).
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for *In vivo* Studies:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Ramel, C. and J. Magnusson (1979). Environ. Health Persp., 31:59-66.

10-July-2001

Appendix B

ROBUST SUMMARY FOR GLUTARIC ACID

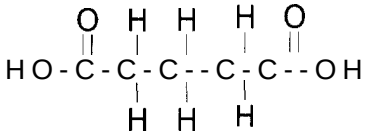
The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as related references in this document.

1.0 Substance Information

CAS Number: 110-94-l

Chemical Name: Pentanedioic acid

Structural Formula:



Other Names: Glutaric acid
Pentandioic acid
1,5-Pentanedioic acid
1,3-Propanedicarboxylic acid
N-pyrotartaric acid

Exposure Limits: No Data.

2.0 Physical – Chemical Properties

2.1 Melting Point

Value:	97.5-98ºC
Decomposition:	No
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Budavari, S. (ed.) (1996). The Merck Index. An Encyclopedia of Chemicals, Drugs. and Biologicals, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point:

Cornils, B. and P. Lappe (1987). cited in Ullmann's Encyclopedia of Industrial Chemistry, 5th ed., pp. 523-539 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

DuPont (1990). Material Safety Data Sheet No. DU000087.

Kühne, R. et al. (1995). Chemosphere, 30(11):2061-2077.

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1873, John Wiley & Sons, Inc., New York.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. G4466 (December 8).

Neumueller, 0. A. (1987). Roempps Chemie-Lexikon, 8 Aufl., Franckh'sche Verlagshandlung, Stuttgart, S. 1511 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., pp. 693-694, Van Nostrand Reinhold Co., New York.

2.2 Boiling Point

Value:	302-304°C
Decomposition:	Very slight decomposition
Pressure:	**760** mm Hg
Method:	No Data
GLP:	Unknown
Reference:	Budavari, S. (ed.) (1996). The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

DuPont (1990). Material Safety Data Sheet No. DU000087.

Neumueller, 0. A. (1987). Roempps Chemie-Lexikon, 8 Aufl., Franckh'sche Verlagshandlung, Stuttgart, S. 15 11 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., pp. 693-694, Van Nostrand Reinhold Co., New York.

2.3 Density

Value:	1.429
Temperature:	15°/4°C
Method:	No Data
GLP:	Unknown

Results:	No additional data.
Reference:	Budavari, S. (ed.) (1996). The Merck Index. An Encyclopedia of Chemicals. Drugs. and Bioloaicals, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available.

Additional References for Density:

Cornils, B. and P. Lappe (1987). cited in Ullmann's Encyclonedia of Industrial Chemistry, 5th ed., pp. 523-539 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

DuPont (1990). Material Safety Data Sheet No. DU000087.

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1873, John Wiley & Sons, Inc., New York.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. G4466 (December 8).

Tao, Y. and P. H. McMurry (1989). Environ. Sci. Technol., 23:1519-1523 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart),

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., pp. 693-694, Van Nostrand Reinhold Co., New York.

2.4 Vapor Pressure

Value:	2.88×10^{-6} mm Hg
Temperature:	25°C
Decomposition:	No Data
Method:	Extrapolated
GLP:	Unknown
Reference:	Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 1: Cl to C4 Compounds, p. 346, Gulf Publ. Co., Houston, TX (SRC Database).
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure:

Grosjean, D. and S. K. Friedlander. In Hidy, G. M. et al. (1980). The Character and Origins of Smog Aerosols, pp. 435-473, John Wiley & Sons, New York (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel,

Wissenschaftliche Verlagsgesellschaft Stuttgart).

Jordan, E. T. (1954). Vapor Pressure of Organic Compounds, Inter-Science Publishers, Inc., New York, NY (ISHOW/305490).

Schaefer, K. and E. Lax (eds.) (1960). Landoldt-Bornstein Numbers and Functions in Physics, Chemistrv, Astronomy, Geophysics. and Technique (Part 2a), Springer-Verlag, Berlin, originally cited in Ludwig and 0. Klemm (1988). Tellus 40B, pp. 340-347 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Stull, D. R. (1947). Ind. Eng. Chem., 39:5 17-540 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Tao, Y. and P. H. McMurry (1989). Environ. Sci. Technol., 23:1519-1523 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

2.5 Partition Coefficient (log Kow)

Value:	-0.29
Temperature:	No Data
Method:	Estimated
GLP:	Unknown
Reference:	Hansch, C. et al. (1995). Exploring QSAR. Hydrophobic, Electronic, and Steric Constants, ACS Prof. Ref. Book, p. 9, American Chemical Society, Washington, DC (HSDB/791).
Reliability:	Not assignable because limited study information was available.

Additional References for Partition Coefficient (log Kow):

BASF AG (n.d.). Untersuchung, Analytisches Labor, unveroeffentlichte Untersuchung (BRU 88.12 1), originally cited in BUA-Kurzbericht Dicarbon-saeuregemisch der BASF AG (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Bayer AG (1992). Berechnung UWS-Produktsicherheit (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Leo, A. J. (1978). Report on the Calculation of Octanol/Water Log p Values for Structures in EPA Files (ISHOW/305492 and 305493).

THOR database POMONA 89, Medchem Software 1989, Daylight Chemical

Information Systems, Claremont, CA 9 17 1 1, USA (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., pp. 693-694, Van Nostrand Reinhold Co., New York.

2.6 Water Solubility

Value:	1.6×10^6 mg/L
Temperature:	28°C
pH/pKa:	No Data
Method:	Measured
GLP:	Unknown
Reference:	Yalkowsky, S. H. and R. M. Dannenfelser (1992). The Aquasol Database of Aqueous Solubility, Version 5, PC version, College of Pharmacy, University of Arizona, Tucson, AZ (SRC Database).
Reliability:	Not assignable because limited study information was available.

Additional References for Water Solubility:

Apelblat, A. and E. Manzurola (1989). J. Chem. Thermodynamics, 2 1: 1005-1008 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Budavari, S. (ed.) (1996) The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12th ed., Merck & Co., Inc., Whitehouse Station, NJ.

Cornils, B. and P. Lappe (1987). cited in Ullmann's Encyclopedia of Industrial Chemistry, 5th ed., pp. 523-539 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

DuPont (1990). Material Safety Data Sheet No. DU000087.

Kühne, R. et al. (1995). Chemosphere, 30(11):206 I-2077.

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1873, John Wiley & Sons, Inc., New York.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. G4466 (December 8).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., pp. 693-694, Van Nostrand Reinhold Co., New York.

2.7 Flash Point: No Data.

2.8 Flammability: No Data.

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	Not Applicable
Temperature:	Not Applicable
Direct Photolysis:	Not Applicable
Indirect Photolysis:	Not Applicable
Breakdown Products:	Not Applicable
Method:	Vapor-phase glutaric acid is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals. The rate constant for the vapor-phase reaction of glutaric acid with photochemically produced hydroxyl radicals has been estimated as $4.2x10^{-12}$ cm^3/molecule-sec using a structure estimation method (SRC AOPWIN v1.90). This corresponds to an atmospheric half-life of about 2.56 days at atmospheric concentration of $1.5x10^6$ hydroxyl radicals per cm^3.
GLP:	Not Applicable
Reference:	SRC AOPWIN Program v 1.90.
Reliability:	Estimated value based on accepted model.

Additional References for Photodegradation: None Found.

3.2 Stability in Water

Concentration:	Not Applicable
Half-life:	Not Applicable
% Hydrolyzed:	Not Applicable
Method:	The Henry's Law constant for glutaric acid is estimated as $1.44x10^{-10}$ atm-m^3/mole from its extrapolated vapor pressure of $2.9x10^{-6}$ mm Hg at 25°C and measured water solubility of $1.6x10^6$ mg/L at 28°C (Yalkowsky and Dannenfelser, 1992). This value indicates that glutaric acid is not expected to rapidly volatilize from water surfaces. Based on this Henry's Law constant, the estimated volatilization half-life from a model river (1 m deep, flowing 1 m/sec, wind velocity 5 m/sec) is approximately $4.9x10^7$ days. The estimated volatilization half-life from a model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec) is approximately $5.4x10^8$ days.

GLP: Not Applicable
Reference: Syracuse Research Corporation EPJWIN v3.05.

Yalkowsky, S. H. and R. M. Dannenfelser (1992). The Aauasol Database of Aqueous Solubility, Version 5, PC Version, College of Pharmacy, University of Arizona, Tucson, AZ (HSDB/791).
Reliability: Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity)

Media: Air, Water, Soil, Sediments
Distributions:
Air: <0.001 %
Water: 42.6 %
Soil: 57.3 %
Sediment: 0.064 %

Adsorption Coefficient: Not Applicable
Desorption: Not Applicable
Volatility: Not Applicable
Method: Calculated according to Mackay, Level III, Syracuse Research Center Epiwin Version 3.05. Emissions (1000 kg/hr) to air, water, and soil compartments using EPA Model defaults.

Data Used:
Molecular Weight: 132.12
Henry's Law Constant: $1.43x10^{-10}$ atm-m^3/mole (HENRYWIN v3.10)
Vapor Pressure: $2.88x10^{-6}$ mm Hg (Yaws, 1994)
Log Kow : -0.29 (Hansch et al., 1995)
Soil Koc : 11.65 (Pckocwin program)
GLP: Not Applicable
Reference: Hansch, C. et al. (1995). Exploring QSAR. Hydrophobic, Electronic, and Steric Constants. ACS Prof. Ref. Book, p. 9, American Chemical Society, Washington, DC (HSDB/791).

Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 1: Cl to C4 Compounds, p. 346, Gulf Publ. Co., Houston, TX (SRC Database).

Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach was developed by Dr. Donald Mackay and

co-workers which is detailed in:

Mackay, D. (1991). Multimedia Environmental Models; The Fugacity Approach, pp. 67- 183, Lewis Publishers, CRC Press.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.

Reliability: Estimated value based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Study No. 1

Value: 6-hour TOD = 0.9%
12-hour TOD = 0.3%
24-hour TOD = 1.4%

Breakdown Products: No Data

Method: The experimental design was based on exposure of the test substance at a concentration of 500 mg/L to activated sludge solids at 2500 mg/L in the Warburg respirometer with oxygen uptake as the measure of oxidation of the compound. Additional details can be found in Gerhold and Malaney, 1966. The theoretical oxygen demand (TOD), defined as the concentration of oxygen in mg/L required to oxidize 500 mg/L of substrate completely, was determined.

GLP: No

Reference: Malaney, G. W. and R. M. Gerhold (1969). J. Water Pollution Control Fed., 41(2):R18-R33.

Gerhold, R. M. and G. W. Malaney (1966). J. Water Pollution Control Fed., 38(4):562.

Reliability: Medium because a suboptimal study design was used and limited study information was available.

Study No. 2

Value: 100% degradation after 7 days; readily biodegradable

Breakdown Products: No Data

Method: Inoculum was predominantly domestic sewage and the concentration was 20 mg/L related to DOC. The modified OECD Screening test, according to 79/83 1 EWG, Annex V,

part C (actualized July 1990), method C.4-B: Modified OECD screening test was performed.

GLP: Unknown

Reference: Bayer AG (n.d.). Untersuchung (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Reliability: Medium because a suboptimal study design was used and limited study information was available.

Additional References for Biodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Chou, W. L. et al. (1978). Biotechnol. Bioeng. Symp., 8:391-414 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Meinck, F. et al. (1970). Les Eaux Residuaires Industrielles (cited in Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., Van Nostrand Reinhold Co., New York, NY).

Jones, H. R. (1971). Environmental Control in the Organic and Petrochemical Industries (cited in Verschueren, K. (1983). Handbook of Environmental Data of Organic Chemicals, 2nd ed., Van Nostrand Reinhold Co., New York, NY).

3.5 Bioconcentration:

Value: BCF 3.162 (log BCF 0.5). This estimated BCF suggests the potential for bioconcentration in aquatic organisms is low.

Method: Bioconcentration factor (BCF) was calculated by BCFWIN Computer Program, Version 2.13, Syracuse Research Corporation. The estimated value was calculated using a log Kow of -0.29 and a regression-derived equation.

GLP: Not Applicable

References: The estimation methodology used by BCFWIN is described in the following document prepared for the U.S. Environmental Protection Agency (OPPT): "Improved Method for Estimating Bioconcentration Factor (BCF) from Octanol-Water Partition Coefficient," SRC TR-97-006 (2nd Update), July 22, 1997; prepared for Robert S. Boethling, EPA-OPPT, Washington, DC, Contract No. 68-D5-0012; prepared by William M. Meylan, Philip H. Howard, Dallas Aronson, Heather Printup, and Sybil Gouchie, Syracuse Research Corp., Environmental Science

Center, 6225 Running Ridge Road, North Syracuse, NY 13212.

Reliability: Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type: **24-hour LC_{50}**
Species: Bluegill sunfish *(Lepomis marochirus)*
Value: **330** mg/L
Method: The methods used were outlined by Freeman, L. (1953). Sewage and Industrial Wastes, 25(7):845. The daily feeding of the fish was discontinued for 24 hours prior to the beginning of the test, and any fish showing signs of being in distress were removed from the tank during this period. The test was conducted in glass jars with a total capacity of 8 L, at 2 1.5-22.0°C. The test solution was prepared and adjusted to temperature in a constant-temperature bath at least 1 hour prior to the beginning of the test. The solution was aerated for at least 10 minutes, or until the dissolved oxygen level reached a minimum of 7-8 ppm. The air stream was then reduced to a rate just sufficient to maintain the dissolved oxygen level.

As soon as 10 fish were placed in the test solution, the time was recorded and the fish were carefully observed for signs of anoxia or any other signs of extreme discomfort. After 24 hours, the fish were checked for the percentage of mortality and the general condition of the survivors.
GLP: Unknown
Test Substance: Glutaric acid, purity not specified
Results: No additional data.
Reference: Dowden, B. F. and H. J. Bennett (1965). J. Water Pollut. Control Fed., 37(9):1308-1316.
Reliability: Low because an inappropriate method or study design was used.

Additional References for Acute Toxicity to Fish: None Found.

4.2 Acute Toxicity to Invertebrates: No Data.

4.3 Acute Toxicity to Aquatic Plants:

Type:	**72-hour EC_{50}**
Species:	*Nitzschia closterium* (marine algae)
Value:	**264** mg/L
Method:	Static; no other data provided.
GLP:	Unknown
Test Substance:	Glutaric acid, purity not specified
Results:	No additional data.
Reference:	Mann, K. and M. Florence (1987). Fuel, 66:404-407 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).
Reliability:	Not assignable because limited study information was available.

Additional Reference for Acute Toxicity to Plants:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Meinck, F. et al. (1978). Biotechnol.. Bioeng. Symp., 8:391-414 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral LD_{50}**
Species/Strain:	Male and female rats/Sprague-Dawley
Value:	2750 mg/kg (95% confidence limits, 2340-3230 mg/kg)
Method:	The method used was similar to OECD Guideline 401, except 5 rats/dose were used. The LD_{50} value was calculated using the method of deBeer.
GLP:	No
Test Substance:	Glutaric acid (tested as a 50% aqueous solution), purity not specified
Results:	The survival time was several hours to 2 days. Mortality ratios were 0/5, 3/5, 3/5, and 5/5 for the 2000, 2510, 3160, and 3980 mg/kg groups, respectively. Tremors were observed in the first 2 hours. Other signs noted included salivation and diarrhea. Necropsy findings included inflammation of gastric mucosa and liver hyperemia.
Reference:	Solutia Inc. (1968). Unpublished Data, YO-68-89.

deBeer, E. J. (1945). J. Pharmacol. Experimen. Ther., 85: 1.

Reliability: High because a scientifically defensible or guideline method was used.

Additional Reference for Acute Oral Toxicity:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Boyland, E. (1940). Biochem. J., 34:1196-1201 (also cited in RTECS/MA3740000).

Type: **Acute Inhalation Toxicity:** No Data.

Type: **Acute Dermal LD_{50}**

Species/Strain: Male and female rabbits/New Zealand White

Value: > 10,000 mg/kg

Method: The minimum lethal dose was determined after 24 hours occlusive skin contact and 14 days of observation. One rabbit/group was tested at concentrations of 1000, 1580, 25 10, 3980, 63 10, and 10,000 mg/kg.

GLP: No

Test Substance: Glutaric acid (tested as a 50% aqueous solution), purity not specified

Results: No deaths occurred. No appreciable toxic signs were noted.

Reference: Solutia Inc. (1968). Unpublished Data, YO-68-89.

Reliability: Medium because a suboptimal study design was used.

Additional References for Acute Dermal Toxicity: None Found.

Type: **Dermal Irritation**

Species/Strain: Rabbits/New Zealand White

Method: On the day prior to study initiation, the hair of 2 male and 4 female rabbits was closely clipped to expose the back from the scapular to the lumbar region. On the day of treatment, each rabbit was placed in a stock that had been fitted with a piece of rubber sheeting. While the animals were in stocks they did not have access to food or water. A 0.5 g aliquot of glutaric acid was applied directly to the test site beneath gauze that was held in place with tape. Three minutes after application of the test material, the test site was evaluated for skin irritation, and then gently washed with warm water. After the 3-minute evaluation, the test material was applied, in the same manner, to 2 other test sites for a 1- or 4-hour exposure period. After application of the test material, the

	rubber sheeting was wrapped around the rabbits and secured with clips to retard evaporation and to keep the test material in contact with the skin without undue pressure. After 1 hour of exposure, the rubber sheeting was loosened, the skin evaluated for irritation, and the test site was gently washed with warm water. The rabbits were wrapped again with the rubber sheeting for an additional 3 hours. Approximately 4 hours after application of the test material, the rubber sheeting was loosened from each animal. The test sites were gently washed with warm water to remove excess test material, and the skin was gently patted dry. Approximately 24 and 48 hours after application of the test material, the test sites were again evaluated for evidence of dermal effects. The scoring system used was the Draize scale.
GLP:	No
Test Substance:	Glutaric acid, purity approximately 97%
Results:	Glutaric acid produced no necrosis throughout the study. Slight erythema was observed in 1 rabbit following a 3-minute, l-hour, or 4-hour exposure to the test material. Slight erythema was still evident in this rabbit 48 hours following application of glutaric acid for 3 minutes. No skin irritation was observed in any of the remaining rabbits throughout the study.
Reference:	DuPont Co. (1987). Unpublished Data, Haskell Laboratory Report No. 261-87.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for Dermal Irritation:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Solutia Inc. (1968). Unpublished Data, YO-68-89.

Type: **Dermal Sensitization:** No Data.

Type:	**Eye Irritation**
Species/Strain:	Rabbits/Strain not specified
Method:	Glutaric acid (100 mg powder) was administered to the eye of 3 rabbits for 24 hours. The eye was then rinsed. The method of testing was the Draize Test.
GLP:	No
Test Substance:	Glutaric acid, purity not specified

Results:	Glutaric acid was irritating to the rabbit eye. The test substance was classified by the EC classification system as irritating. Scores of PII=35.2/110.0 were reported. Copious discharge, moderate erythema and edema, mild eversion of lids, and iritial dullness were observed during the 1st hour. Mild erythema, slight edema, and slight dullness remained at the final reading after 7 days.
Reference:	Solutia Inc. (1968). Unpublished Data, YO-68-89.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Acute Eye Irritation: None Found.

5.2 Repeated Dose Toxicity

Study No. 1

Type:	**Subchronic Oral Feeding Study**
Species/Strain:	Rat/Sprague-Dawley
Sex/Number:	Male and female/l5 per sex per test group
Exposure Period:	90 days
Frequency of Treatment:	Daily
Exposure Levels:	0, 0.5, 1.0, 2.0%
Method:	The test method was similar OECD Guideline 408 with some exceptions. Fifteen males and 15 females per test group were used. Food consumption was calculated for 5 males and 5 females per group. Body weights, mortality and reactions were recorded. Hematology (hct, rbc, hgb, tot. & diff. leuk), blood chemistry (BUN, SAP, SGPT, GLU), and urinalysis (glu, alb. pH, spec. g, micros. elements) were recorded for 5 males and 5 females from the high dose group (2%) and control group (0%) at 45 and 84 days on test. Organ weights and ratios (brain, liver, kidneys, spleen, gonads, heart) from all survivors were recorded at terminal sacrifice. Histopathology was conducted on 40 tissues/organs for 10 males and 10 females from the high dose group (2%) and control (0%) group.
GLP:	No
Test Substance:	Glutaric acid, purity not specified
Results:	No treatment-related mortality was found. Statistically significantly reduced weight gain in the 2% females and depression in weight gain of the 2% males (not statistically significant) were observed. Food consumption was normal in all groups. No differences were noted in hematology, clinical chemistry, or urinalysis. There were no histopathological findings or organ weight changes attributable to the test substance.

	The NOAEL was ≥ 1% and the LOAEL was 2%.
Reference:	Solutia Inc. (1968). Unpublished Data, BT-68-26A.
Reliability:	High because a scientifically defensible or guideline method was used.

Study No. 2

Type:	**Subchronic Oral Feeding Study**
Species/Strain:	Dog/Beagle
Sex/Number:	Male and female/4 per sex per test group
Exposure Period:	90 days
Frequency of Treatment:	Daily
Exposure Levels:	0, 1, 3, 5% (for days I-10) 0, 0.5, 1, 2% (for days 1 l-90)
Method:	Body weights, food consumption, mortality, and physical signs were recorded. Hematology (hct, hgb, rbc, tot. & diff. leuk), blood chemistry (BUN, SAP, SGPT, SGOT, GLU), and urinalysis (pH, spec. g, glu, micros.) were recorded at 45 and 85 days. At terminal sacrifice, all dogs had organ weight/ratios (liver, kidney, heart, brain, spleen, gonads, adrenals, thyroid, and pituitary) recorded. Histopathology was conducted on approximately 40 organs/tissues.
GLP:	No
Test Substance:	Glutaric acid, purity not specified
Results:	Body weight loss was observed in the 5% male and female groups and in the 3% female group after 10 days. Reduced food consumption paralleled weight loss. Overall study weight gains for the low dose and mid dose groups were equal to the control group, while the high dose group had 5/8 dogs without weight gain. No treatment-related effects were seen in any other study parameters. The NOAEL was ≥2% and the LOAEL was 3%.
Reference:	Solutia Inc. (1968). Unpublished Data, BT-68-26B.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Repeat Dose Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Solutia Inc. (1977). Unpublished Data, BD-77- 16A.

Solutia Inc. (1977). Unpublished Data, BD-77-17A.

DuPont Co. (1944). Unpublished Data, Haskell Laboratory Report No. 14-44.

5.3 Developmental Toxicity

Study No. 1

Species/Strain:	Rats/CD@
Sex/Number:	Females/25 per group
Route of Administration:	Gavage
Frequency of Treatment:	Daily
Exposure Period:	Gestation Days 6-15, Cesarean section Day 20
Exposure Levels:	0, 125,400, 1300 mg/kg
Method:	Male rats were 125 days old and mature virgin females were approximately 7 1 days old. Body weights of the female rats ranged from 190-262 g on Day 0 of pregnancy. Each male was housed nightly with up to 3 females until mating was completed. Vaginal washings were made on the morning after each exposure to a male, and the day of positive identification of spermatozoa in the washing was designated as day 0 of pregnancy (gestation day 0). Body weights were measured periodically during gestation, and the animals were observed daily for signs of toxicity. On gestation day 20, females were sacrificed and examined for gross pathologic changes. Reproductive status was determined. Corpora lutea, implantation sites, number of fetuses (live and dead), and resorptions (early and late) were recorded. All fetuses were weighed and examined externally. Fetuses of 1/3 of the litters were examined for visceral abnormalities. Fetuses in the remaining 2/3 of the litters were examined for skeletal abnormalities.
GLP:	Yes
Test Substance:	Glutaric acid, purity approximately 98%
Results:	No adverse effects were observed on body weight, general appearance, or behavior of rats at 125 mg/kg. At 400 mg/kg, no effect on body weight was observed, but salivation, rales, and nasal discharge were observed. At 1300 mg/kg, 1 death occurred (gestation day 10) and 1 animal was sacrificed early (gestation day 13). Mean body weight gains were decreased at 1300 mg/kg during the dosing period. The mean body weight gains post-dosing (gestation days 15-20) were normal compared to control, indicating a reversible effect on body weight after test substance withdrawal. Clinical signs observed at 1300 mg/kg included salivation, rales, nasal discharge, slight

inactivity, labored breathing, decreased body temperature,, soft stools, and staining around the mouth, nares, and anogenital area.

No adverse effects on pregnancy, and no teratogenic effects were observed at any level tested. A significant increase in the number of resorptions at 1300 mg/kg was observed compared to control. The number or resorptions was within normal expected limits; therefore, the increase was not considered biologically meaningful. A summary of reproductive outcomes is provided in the table below. All parameters, except pregnancy rate and sex ratio, are reported as means/litter.

Concentration (mg/kg):	0	125	400	1300
Pregnancy Rate (%):	72	80	84	88
Corpora lutea:	15	15	15	15
Implantations:	13	14	14	13
No. of Resorptions:	0.4	0.9	0.5	1.0
Total No. of Fetuses:	13	13	13	12
Mean Fetal Weight (g):	3.6	3.7	3.7	3.6
Sex Ratio (% male/female):	52/48	48/52	51/49	52/48

Reference: Sterling-Winthrop Research Institute (1984). Unpublished Data.

Bradford, J. C. et al. (1984). Teratology, 29(2): 19A.

Reliability: High because a scientifically defensible or guideline method was used.

Study No. 2

Species/Strain: Rabbits/New Zealand White

Sex/Number: Females/l 8 per group

Route of Administration: Gavage

Frequency of Treatment: Daily

Exposure Period: Gestation Days 6-18, Cesarean section Day 29

Exposure Levels: 0, 50, 160,500 mg/kg

Method: The rabbits used in the study were sexually mature stockbreeder

males and sexually mature virgin females. The females were approximately 4-6 month of age, and their body weights ranged from 3 .O-5.1 kg on gestation day 0. Each female was placed in a mating cage with a male (usually once in the morning and again in the afternoon) and after observation of copulation, vaginal smears were made and examined for the presence of motile spermatozoa (gestation day 0). Body weights, food consumption, and clinical signs were recorded. On gestation day 29 the females were sacrificed and examined for gross pathologic changes. Reproductive status was determined. Corpora lutea, implantation sites, number of fetuses (live and dead), and resorptions (early and late) were recorded. All fetuses were weighed and given external, visceral, and skeletal examinations for abnormalities.

GLP: Yes

Test Substance: Glutaric acid, purity >98%

Results: No test substance-related mortality was observed. No changes in body weights or clinical signs were observed in females at any level tested. No adverse effects on pregnancy, and no embryotoxic or teratogenic effects were observed. A summary of reproductive outcomes is provided in the table below. All parameters, except pregnancy rate and sex ratio, are reported as means/litter.

Concentration (mg/kg):	0	50	160	500
Pregnancy Rate % :	94	94	a3	83
Corpora lutea:	10	11	9	10
Implantations:	8	9	7	8
No. of Resorptions:	1.8	0.5	0.8	0.6
Total No. of Fetuses:	6	9	6	8
Mean Fetal Weight (g):	40.5	39.4	41.3	41.5
Sex Ratio (% male/female):	44/56	50/50	50/50	45/55

Reference: Sterling-Winthrop Research Institute (1984). Unpublished Data.

Bradford, J. C. et al. (1984). Teratology, 29(2):19A.

Reliability: High because a scientifically defensible or guideline method was used.

Study No. 3

Species/Strain:	Rat/Sprague-Dawley
Sex/Number:	Female/5 per group
Route of Administration:	Gavage
Exposure Period:	Days 6- 15 of gestation
Frequency of Treatment:	Daily
Exposure Levels:	0, 100, 300, 1000 mg/kg
Method:	This pilot study was conducted with 5 pregnant rats per test group. Distilled water was used as the vehicle. Maternal indices measured included pregnancy rate, mortality rate, physical observations, and body weight. Reproductive data recorded included resorptions, implantations, corpora lutea, fetal survival, and fetal necropsy. Females were sacrificed at day 21 of gestation.
GLP:	No
Test Substance:	Glutaric acid, purity not specified
Results:	Slightly lower mean body weight changes were noted during the dosing period for all treatment groups. No other study parameters were remarkable. The NOAEL for maternal toxicity was $\geq$ 1000 mg/kg.
Reference:	Solutia Inc. (1977). Unpublished Data, BD-77-20A.
Reliability:	Low because an inappropriate method or study design was used. A small number of animals/group were used and limited fetal exams were conducted.

Additional References for Developmental Toxicity: None Found.

5.4 **Reproductive Toxicity:** No Data.

5.5 Genetic Toxicity

Type:	**In vitro Bacterial Reverse Mutation Assay**
Tester Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538
Exogenous Metabolic Activation:	With and without rat liver microsomes
Exposure Concentrations:	Assay 1: 0, 0.5, 5, 50, 500, 5000 µg/plate (without activation) Assay 2: 0, 1000, 2000, 3000, 4000, 5000 µg/plate (without activation) Assay 3: 0, 0.5, 5, 50, 500, 5000 µg/plate (with activation)

Method:	Glutaric acid was examined by the *in vitro* *Salmonella*/microsome mutagenicity test (Ames test). Concurrent positive and negative controls were tested. The negative controls were water and dimethyl sulfoxide (DMSO). The positive controls included 2-nitrofluorine, N-methyl-N-nitro-N-nitrosoguanidine, 2-aminofluorene, 8-aminoquinoline, and 2-anthramine.
GLP:	No
Test Substance:	Glutaric acid, purity not specified
Results:	Negative
Remarks:	In the 1st non-activation assay, the highest concentration of glutaric acid (5000 µg/plate) was inhibitory to all 5 *Salmonella* tester strains. In the 2nd non-activation assay with *3 Salmonella* tester strains (TA98, TA1537, and TA1538), inhibition of the background *Salmonella* lawn tester strains occurred at 2000 µg/plate. Glutaric acid did not precipitate in the agar overlay at any of the concentrations tested. With the exception of the 5000 µg/plate concentration of glutaric acid with *Salmonella* strain TA100 in the metabolic activation assay, none of the 2 highest tested doses of glutaric acid were toxic to the *Salmonella* strains. The test substance was partially toxic at 5000 µg/plate to *Salmonella* TA100. Precipitation due to glutaric acid was not noted at any concentration in the top agar overlay. Under the conditions of this test, glutaric acid was not mutagenic for any of the 5 Salmonella tester strains, in either the non-activation or metabolic activation systems.
Reference:	Sterling-Winthrop Research Institute (1978). Unpublished Data. Bradford, J. C. et al. (1984). Teratology, 29(2): 19A.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for In *vitro* Bacterial Reverse Mutation Assay:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Sterling-Winthrop Research Institute (198 1). Unpublished Data, study contracted to Pharmakon Laboratories.

Sakagami, Y. et al. (1988). Mutat. Res., 209(3-4):155-160.

Sterling-Winthrop Research Institute (198 1). Unpublished Data.

Type:	***In* vitro Mouse Lymphoma Forward Mutation Assay**
Cell Type:	Mouse lymphoma cells (L5 178Y; TK locus)
Exogenous Metabolic Activation:	With Aroclor-induced rat liver S-9
Exposure Concentrations:	Test 1: 0, 156,624, 1249, 2498, 3997, 4996 µg/mL Test 2: 0, 2573, 3431, 4288, 5146, 6861 µg/mL Test 3: 0, 4977, 5806, 6636, 7465, 8295 µg/mL
Method:	The method of Clive and Spector, 1975, was performed. One or 2 replicates were performed for tests 1 and 2, and 3 replicates were performed for test 3. Concurrent negative and positive controls were tested. The negative control was water and the positive control was dimethylnitrosamine.
GLP:	Yes
Test Substance:	Glutaric acid, purity not specified
Results:	Negative
Remarks :	Glutaric did not produce repeatable increases in mutant frequency at the TK locus in L5 178Y mouse lymphoma cells under the conditions of S-9 microsomal activation and adjustment of the assay mixture to a neutral pH range (pH 7.0 to pH 7.4). Concentrations from 156-8295 µg/mL (with pH adjustment) induced, at best, moderate toxicity. Sporadic increases in mutant frequency were observed, but could not be confirmed in replicate treatments and/or at higher concentrations of the test substance. Therefore, at high concentrations, glutaric acid is considered to be inactive under activation conditions in the mouse lymphoma forward mutation assay.
Reference:	Clive, D. and J. F. S. Spector (1975). Mutat. Res., 3 1: 17-29. Sterling-Winthrop Research Institute (198 1). Unpublished Data, study contracted to Litton Bionetics. Bradford, J. C. et al. (1984). Teratology, 29(2):19A.
Reliability:	High because a scientifically defensible or guideline method was used.

Type:	**InVitro Transformation of Balb/3T3 Cells Assay**
Cell Type:	Mouse Balb/3T3
Exogenous Metabolic Activation:	With and without rat liver microsomes
Exposure	Trial 1: 0, 0.81, 3.3, 6.7, 10, 12.5 mg/mL, non-activation

Concentrations:	Trial 2: 0, 3.3, 6.7, 10 mg/L, non-activation Trial 3: 0, 3.3, 6.7, 10 mg/L, non-activation Tria14: 0, 5.6, 11.2, 16.8, 21, 26.3 mg/L, activation
Method:	The procedure used was based on that reported by Kakunaga, 1973. Twenty-four hours prior to treatment, a series of 60 mm dishes were seeded with 10^4 cell/dish and incubated. At least 20 dishes were then treated for each of the following conditions: 5 preselected doses of test substance; positive control; and solvent negative control. The dishes were incubated for a 72-hour exposure period; the cells were then washed and incubation was continued for approximately 4 weeks with refeeding twice a week. The assay was terminated by fixing the cell monolayers with methanol and staining with Giemsa. The stained dishes were examined by eye and by microscope to determine the number of foci of transformed cells. Three trials were performed without activation and a 4^{th} trial was performed with activation using rat liver microsomes. Twenty replicates per concentration were performed. Concurrent negative and positive controls were run. The negative controls were media or dimethyl sulfoxide (DMSO). The positive controls included 3-methylcholanthrene (MCA) or dimethylnitrosamine. In general, a response at only 1 dose level just attaining the 95% confidence level was not considered sufficient evidence for activity in the assay. However, responses at 1 or more treatment levels attaining the 95% confidence level and exhibiting evidence of dose dependency were considered as positive evidence of transforming activity, and responses achieving the 99% confidence level over 1 or more test substance treatments were similarly interpreted.
GLP:	Yes
Test Substance:	Glutaric acid, purity not specified
Results:	Positive
Remarks:	Glutaric acid induced the appearance of a significant number of transformed foci under nonactivaiton and under S-9 activation conditions. The active concentrations under nonactivation conditions ranged from 3.3- 12.5 mg/mL, and the observed activity was reproducible for the 6.7 and 10 mg/mL treatments. In the presence of an S-9-mediated activation system, 3T3 cell transforming activity was observed for the test substance treatments of 16.8 and 21 mg/mL. Evidence that the observed responses were dose related was obtained under nonactivation and under S-9

activation conditions. Therefore, the test material was considered to be active in the Balb/c-3T3 *in vitro* transformation assay in the absence and presence of an exogenous metabolic activation system.

Reference: Sterling Winthrop Research Institute (1983). Unpublished Data, contracted to Litton Bionetics.

Bradford, J. C. et al. (1984). Teratology, 29(2): 19A.

Kakunaga, T. (1973). Int. J. Cancer, 12:463-473.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for In *vitro* Clastogenicity Studies:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Sterling-Winthrop Research Institute (1980). Unpublished Data, study contracted to Litton Bionetics.

Bradford, J. C. et al. (1984). Teratology, 29(2):19A.

Type: **In *vivo* Mouse Micronucleus Assay**
Species/Strain: Mouse/CD- 1
Sex/Number: Males and females/4 per sex per concentration
Route of Administration: Intraperitoneal injection
Concentrations: 0,800 mg/kg
Method: Two groups of animals (11 weeks old) were given a single intraperitoneal injection at 800 mg/kg and sacrificed at 30 or 48 hours. Two additional groups of animals were given 2 injections of 800 mg/kg at 0 and 24 hours and sacrificed at 48 or 72 hours, respectively, after the first dose. Similar groups, serving as the positive and negative control, were evaluated concurrently. The positive control was administered as a single dose of triethylenemelamine (TEM), and the animals were sacrificed at 30 hours. The negative control animals were administered 2 injections of distilled water at 0 and 24 hours, and these animals were sacrificed 48 hours after the initial dose. Slides were prepared from the bone marrow of the femurs of each animal in the assay and stained. Coded slides were scored for the number of polychromatic erythrocytes (PCE) with micronuclei in 1000 PCE.

	Assessment of the test substance as positive was based on its ability to produce a statistically significant increase in the number of micronuclei in polychromatic erythrocytes as compared to the negative control.
GLP:	Yes
Test Substance:	Glutaric acid, purity not specified
Results:	Negative
Remarks:	Glutaric acid did not produce a statistically significant increase in micronuclei in any of the treated groups, and was determined to be negative in this assay.
Reference:	Sterling-Winthrop Research Institute (1983). Unpublished Data, study contracted to Pharmakon Research International, Inc. Bradford, J. C. et al. (1984). Teratology, 29(2): 19A.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for In *vivo* Studies: None Found.

Appendix C

10-July-2001

ROBUST SUMMARY FOR SUCCINIC ACID

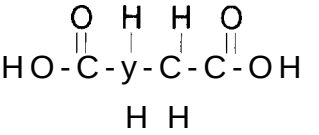
The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as related references in this document.

1.0 Substance Information

CAS Number: 110-15-6

Chemical Name: Butanedioic acid

Structural Formula:



Other Names: Succinic acid
Amber acid
Asuccin
1,4-Butanedioic acid
Dihydrofumaric acid
Ethylene dicarboxylic acid
1,2-Ethanedicarboxylic acid
Ethylenesuccinic acid
Wormwood
Wormwood acid

Exposure Limits: No Data.

2.0 Physical – Chemical Properties

2.1 Melting Point

Value:	185187°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Budavari, S. (ed.) (1996). The Merck Index. An Encyclopedia of Chemicals, Drugs, and Bioloaicals, 12th ed., p. 9040, Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point:

Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3571, John Wiley and Sons, Inc., New York, NY.

DuPont Co. (1989). Material Safety Data Sheet No. DU000085.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 1057, John Wiley and Sons, Inc., New York, NY.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 33 15, John Wiley and Sons, Inc., New York, NY.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. S7226 (December 8) (MALLIN/2767).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY.

2.2 Boiling Point

Value:	235°C
Decomposition:	Yes; partial conversion into the anhydride
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Budavari, S. (ed.) (1996). The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12th ed., p. 9040, Merck & Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3571, John Wiley and Sons, Inc., New York, NY.

DuPont Co. (1989). Material Safety Data Sheet No. DU000085.

Lewis, R. J., Sr. (1997). Hawlev's Condensed Chemical Dictionary, 13th ed., p. 1057, John Wiley and Sons, Inc., New York, NY.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 33 15, John Wiley and Sons, Inc., New York, NY.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. S7226

(December 8) (MALLIN/2767).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY.

2.3 Density

Value:	1.564
Temperature:	15°/4°C
Method:	No Data
GLP:	Unknown
Results:	No additional data.
Reference:	Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 3315, John Wiley and Sons, Inc., New York, NY.
Reliability:	Not assignable because limited study information was available.

Additional References for Density:

Budavari, S. (ed.) (1996). The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12th ed., p. 9040, Merck & Co., Inc., Whitehouse Station, NJ.

Clayton, G. D. and F. E. Clayton (1994). Pattv's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3571, John Wiley and Sons, Inc., New York, NY.

DuPont Co. (1989). Material Safety Data Sheet No. DU000085.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 1057, John Wiley and Sons, Inc., New York, NY.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. S7226 (December 8) (MALLIN/2767).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY.

2.4 Vapor Pressure

Value:	1.9×10^{-7} mm Hg
Temperature:	25°C
Decomposition:	No Data
Method:	Extrapolated
GLP:	Unknown
Reference:	Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 1

Cl to C4 Compounds, p. 346, Gulf Publ. Co., Houston, TX (HSDB/791).

Reliability: Not assignable because limited study information was available.

Additional References for Vapor Pressure:

Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3571, John Wiley and Sons, Inc., New York, NY.

DuPont Co. (1989). Material Safety Data Sheet No. DU000085.

2.5 Partition Coefficient (log Kow)

Value:	-0.59
Temperature:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Verschueren, K. (1983). Handbook of Environmental I ata on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY.
Reliability:	Not assignable because limited study information was available.

Additional References for Partition Coefficient (log Kow):

Collander, R. (1951). Acta Chem. Scand., 5:774-780 (ISHOW/IS-0005386)

Hansch, C. et al. (1995). Exploring QSAR. Hydrophobic, Electronic, and Steric Constants, ACS Prof. Ref. Book, p. 9, American Chemical Society, Washington, DC (HSDB/791).

Leo, A. J. (1978). Report on the Calculation of Octanol/Water Log P Values for Structures in EPA Files (ISHOW/IS-0005385).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY.

2.6 Water Solubility

Value:	8.3×10^4 mg/L
Temperature:	25°C
pH/pKa:	No Data
Method:	Measured
GLP:	Unknown
Reference:	Yalkowsky, S. H. and R. M. Dannenfelser (1992). The

Aauasol Database of Aqueous Solubility, Version 5, PC Version, College of Pharmacy, University of Arizona, Tucson, AZ (SRC Database).

Reliability: Not assignable because limited study information was available.

Additional References for Water Solubility:

Budavari, S. (ed.) (1996). The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12th ed., p. 9040, Merck & Co., Inc., Whitehouse Station, NJ.

Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3571, John Wiley and Sons, Inc., New York, NY.

DuPont Co. (1989). Material Safety Data Sheet No. DU000085.

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 1 3th ed., p. 1057, John Wiley and Sons, Inc., New York, NY.

Lewis, R. J. Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 3315, John Wiley and Sons, Inc., New York, NY.

Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. S7226 (December 8) (MALLIN/2767).

Stephan, H. and T. Stephen (1963). Solubilities of Inorganic and Organic Compounds, Vol. I. Binary Systems, Macmillan Co., New York, NY (ISHOW/IS-0005384).

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY,

2.7 Flash Point

Value:	160°C
Method:	Open Cup
GLP:	Unknown
Reference:	DuPont Co. (1989). Material Safety Data Sheet No. DU000085.
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point: None Found.

2.8 Flammability

Results:	As with most organic solids, tire is possible at elevated temperatures or by contact with an ignition source.
Method:	No Data
GLP:	Not Applicable
Reference:	Mallinckrodt Baker, Inc. (1996). Material Safety Data Sheet No. S7226 (December 8) (MALLIN/2767).
Reliability:	Not assignable because limited study information was available.

Additional Reference for Flammability:

Lewis, R. J., Sr. (1997). Hawley's Condensed Chemical Dictionary, 13th ed., p. 1057, John Wiley and Sons, Inc., New York, NY.

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	Not Applicable
Temperature:	Not Applicable
Direct Photolysis:	Not Applicable
Indirect Photolysis:	Not Applicable
Breakdown Products:	Not Applicable
Method:	According to a model of gas/particle partitioning of semivolatile organic compounds in the atmosphere (Bidleman, 1988), succinic acid, which has an extrapolated vapor pressure of 1.9×10^{-7} mm Hg at 25°C (Yaws, 1994), will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase succinic acid is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals (SRC, n.d.). The rate constant for the vapor-phase reaction of succinic acid with photochemically-produced hydroxyl radicals has been estimated as 2.8×10^{-12} cm^3/molecule*sec at 25°C (SRC, n.d.) using a structure estimation method (Meylan and Howard, 1993; SRC, n.d.). This corresponds to an atmospheric half-life of about 5.8 days at an atmospheric concentration of 5×10^5 hydroxyl radicals/cm^3 (Meylan and Howard, 1993; SRC, n.d.). Particulate-phase succinic acid may be physically removed from the air by wet and dry deposition (SRC, n.d.).
GLP:	Not Applicable

Reference: Bidleman, T. F. (1988). Environ. Sci. Technol., 22:361-367 (HSDB/791).

Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 1: Cl to C4 Compounds, p. 346, Gulf Publ. Co., Houston, TX (HSDB/791).

SRC (Syracuse Research Corporation) (n.d.). (HSDB/791).

Meylan, W. M. and P. H. Howard (1993). Chemosphere, 26:2293-2299 (HSDB/791).

Reliability: Estimated value based on accepted model.

Additional References for Photodegradation: None Found.

3.2 Stability in Water

Concentration: Not Applicable
Half-life: Not Applicable
% Hydrolyzed: Not Applicable
Method: Succinic acid is not expected to undergo hydrolysis (SRC, n.d.) in the environment due to the lack of functional groups to hydrolyze (Lyman et al., 1990). The rate constant for the reaction of succinic acid with hydroxyl radicals in aqueous solution has been measured as 3.1×10^{8} L/mol sec (Buxton et al., 1988). This corresponds to a half-life of about 7.1 years (SRC, n.d.) at an average aqueous hydroxyl radical concentration of 1×10^{-17} mol/L (Mill et al., 1980).

The Henry's Law constant for succinic acid is estimated as 3.6×10^{-13} atm-m^3/mole (SRC, n.d.) from its extrapolated vapor pressure, 1.9×10^{-7} mm Hg (Yaws, 1994), and measured water solubility, 8.3×10^{4} mg/L (Yalkowsky and Dannenfelser, 1992). This value indicates that succinic acid will be essentially nonvolatile from water surfaces (Lyman et al., 1990; SRC, n.d.). pKa's of 4.2 and 5.6 for succinic acid (Dean, 1987) also indicate that succinic acid will be essentially nonvolatile from water surfaces, as it will exist primarily in the ionized form under environmental pHs (SRC, n.d.).

GLP: Not Applicable
Reference: Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 1: Cl to C4 Compounds, p. 346, Gulf Publ. Co., Houston, TX (HSDB/791).

Yalkowsky, S. H. and R. M. Dannenfelser (1992). The

Aquasol Database of Aqueous Solubility, Version 5, PC Version, College of Pharmacy, University of Arizona, Tucson, AZ (HSDB/791).

Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 15-l to 15-29, American Chemical Society, Washington, DC (HSDB/791).

Dean, J. A. (1987). Handbook of Organic Chemistry, p. 8-50, McGraw-Hill, Inc., New York, NY (HSDB/791).

Buxton, G. V. et al. (1988). J. Phys. Chem. Ref. Data, 17:513-882 (HSDB/791).

Mill, T. et al. (1980). Science, 207:886-887 (HSDB/791).

SRC (Syracuse Research Corporation) (n.d.). (HSDB/791).

Reliability: Estimated value based on accepted model.

Additional References for Stability in Water: None Found.

3.3 Transport (Fugacity)

Media:	Air, Water, Soil, Sediments	
Distributions:	Air:	<0.001%
	Water:	42.7 %
	Soil:	57.2 %
	Sediment:	0.06 %
Adsorption Coefficient:	Not Applicable	
Desorption:	Not Applicable	
Volatility:	Not Applicable	
Method:	Calculated according to Mackay, Level III, Syracuse Research Corporation Epiwin Version 3.05. Emissions (1000 kg/hr) to air, water, and soil compartments using EPA model defaults.	
	Data Used:	
	Molecular Weight: 118.09	
	Henry's Law Constant: 2.077×10^{-11} atm-m^3/mole (Suntio et al., 1988)	
	Vapor Pressure: 1.91×10^{-7} mm Hg (Yaws, 1994)	
	Log Kow : -0.59 (Suntio et al., 1988)	
	Soil Koc : 6.3 14 (Pckocwin program)	
GLP:	Not Applicable	
Reference:	Suntio, L. R. et al. (1988). Chemosphere, 17: 1249-1290.	

Yaws, C. L. (1994). Handbook of Vapor Pressure, Vol. 1: Cl to C4 Compounds, p. 346, Gulf Publ. Co., Houston, TX.

Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach was developed by Dr. Donald Mackay and co-workers which is detailed in:

Mackay, D. (199 1). Multimedia Environmental Models; The Fugacity Approach, pp. 67-l 83, Lewis Publishers, CRC Press.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.

Reliability: Estimated value based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Study No. 1

Value: 67.5% of BODT in 5 days with sewage sludge; 52 to 89% biodegradation in 7 days in soil studies.

Breakdown Products: No Data

Method: In Warburg studies using a sewage seed, succinic acid reached 67.5% of its theoretical BOD in 5 days. In Warburg studies, succinic acid (500 ppm) reached 11.2%, 27.2%, and 42.4% of its theoretical BOD in 6, 12, and 24 hours with activated sludge inoculum; while cultures acclimated to phenol reached 57% of BODT after 12 hours. Succinic acid, at an initial concentration of 1000 ppm, has been observed to biodegrade in soil at rates ranging from 52 to 89% in 7 days to 71 to 95% in 84 days (HSDB/791).

GLP: Unknown

Reference: Heukelekian, H. and M. C. Rand (1955). J. Water Pollut. Contr. Assoc., 27:1040-1053 (also cited in BIODEG/BD-000 1906).

Reliability: Medium because a suboptimal study design was used.

Study No. 2

Value: 6-hour TOD = 0.9%
12-hour TOD = 0.3%

	24-hour TOD = 1.4%
Breakdown Products:	No Data
Method:	The experimental design was based on exposure of the test substance at a concentration of 500 mg/L to activated sludge solids at 2500 mg/L in the Warburg respirometer with oxygen uptake as the measure of oxidation of the compound. Additional details can be found in Gerhold and Malaney, 1966. The theoretical oxygen demand (TOD), defined as the concentration of oxygen in mg/L required to oxidize 500 mg/L of substrate completely, was determined.
GLP:	No
Reference:	Malaney, G. W. and R. M. Gerhold (1969). J. Water Pollution Control Fed., 41(2):R18-R33. Gerhold, R. M. and G. W. Malaney (1966). J. Water Pollution Control Fed., 38(4):562.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Biodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Chou, W. L. et al. (1979). Biotechnol. Bioeng. Symp., 8:391-414 (HSDB/791).

Dore, M. et al. (1975). Trib. Cebedeau, 28:3-1 1 (BIODEG/BD-0001905).

Hammond, M. W. and M. Alexander (1972). Environ. Sci. Technol., 6(5):732-735 (cited in Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY).

Huddleston, R. L. et al. (1986). Water Resour. Symp. 13 (Land Treat: Hazard. Waste Manage. Altern.):41-61 (HSDB/791).

Jones, H. R. (1971). Environmental Control in the Organic and Petrochemical Industries, Noyes Data Corporation (cited in Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY).

McKinney, R. E. et al. (1956). Sew. Indust. Wastes, 28:547-557 (BIGDEGIBD-0001908).

Meinck, G. et al. (1970). Les Eaux Residuaires Industrielles (cited in

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY.

Speece, R. E. (1983). Environ. Sci. Technol., 17:416A-427A (HSDB/791).

Takemoto, S. et al. (1981). Suishitsu Odaku Kenkyu, 4:80-90 (BIODEG/BD-000 19 19).

Tate, R. L. III (1979). Appl. Environ. Micro., 37: 1085-1090 (BIODEG/104249).

Zobell, C. E. (1940). Biol. Bull., 78:388 (cited in Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold Co., New York, NY).

3.5 Bioconcentration

Value:	BCF 0.21. According to a classification scheme (Franke et al., 1994), this BCF value suggests that bioconcentration in aquatic organisms is low (SRC, n.d.).
Method:	The estimated value was calculated using a measured log Kow of -0.59 (Hansch et al., 1995) and a recommended regression-derived equation (Lyman et al., 1990).
GLP:	Not Applicable
Reference:	Hansch, C. et al. (1995). Exploring QSAR. Hydronhobic, Electronic, and Steric Constants, ACS Prof. Ref. Book, p. 9, American Chemical Society, Washington, DC (HSDB/791). Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 5-4, 5-10, American Chemical Society, Washington, DC (HSDB/791). Franke, C. et al. (1994). Chemosphere, 29: 1501- 1504 (HSDB/791). SRC (Syracuse Research Corporation) (n.d.). (HSDB/791).
Reliability:	Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type:	**24-hour Toxicity**
Species:	*Ptychocheilus oregonensis* (Northern squawfish) *Oncorhynchus tshawytscha* (Chinook salmon) *Oncorhynchus kisutch* (Coho salmon, silver salmon)

Value:	> 10 or 15 ppm
Method:	The fish used measured 5-10 cm. A series of insulated, round, stainless steel tubs were used for water baths. The water was obtained from Rochat Creek, and a chemical analysis of the water was made during summer when the stream flows were low. The pH of the water was 7.2, alkalinity was 7 ppm, and hardness was O-I 7 ppm. The baths were served by a common refrigerated reservoir through which temperature-controlled water was recirculated. Each tub held 9.5 L plastic aquaria, and each aquarium was aerated by a single stone air-breaker and lined with a disposable polyethylene poultry bag. The bag was closed at the top to prevent fish from escaping. Fish were acclimatized at about the temperatures of the assay vessels. The acclimatizing period varied from 3-24 hours, but most fish were conditioned at least overnight. The test fish were starved during acclimatization and transferred to the assay vessel approximately 2 hours prior to addition of 10 ppm of test substance. Usually 1 squawfish and 1 each of 2 species of salmonid were placed together in 1 vessel in 4 L of water, the load being approximately 5 g of fish/L solution. Water temperature was taken several times during each test, with only the highest temperature recorded in a 24-hour test period reported. The times at which a fish lost its equilibrium and died were recorded. Equilibrium was defined as lost when a fish was no longer able to remain right-side-up, and death was designated when a fish ceased visible movement.
GLP:	No
Test Substance:	Succinic acid, purity not specified
Results:	In *Ptychocheilus oregonensis*, loss of equilibrium occurred in 4-8 hours at 10 ppm, but was regained by 17 hours. No deaths were reported. At 15 ppm neither loss of equilibrium nor death occurred. In *Oncorhynchus tshawytscha* and *kisutch,* neither loss of equilibrium nor death occurred at 10 or 15 ppm.
Reference:	MacPhee, C. and R. Ruelle (1969). Univ. of Idaho Forest, Wildl. Range Exp. Station Bull. No. 3, Moscow, ID.
Reliability:	Low because an inappropriate method or study design was used.

Additional References for Acute Toxicity to Fish: None Found.

4.2 Acute Toxicity to Invertebrates

Type:	**48-hour EC_{50}**
Species:	*Daphnia magna*
Value:	374.2 mg/L (95% confidence limits, 350-400 mg/L)
Method:	Dilution water from a local spring-fed pond was used as culture media and for toxicity tests. The water was relatively hard, averaging 154.5 mg/L of hardness measured as $CaCO_3$ over the period of use. In addition, the following averages for the spring water were reported: pH of 7.7, alkalinity of 137.7 mg/L as $CaCO_3$, conductivity of 290.4 µmohs/cm, Ca of 32.7 mg/L, Mg of 19.7 mg/L, Na of 2.4 mg/L, and K of 1.3 mg/L. The acute static tests were conducted as described in EPA (1975). Ecological Research Series, EPA-600/3-75-009 ("Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians"). First instar *Daphnia* were used for all tests. The tests were conducted in duplicate for 48 hours at 22°C in a constant-temperature chamber. All test substance concentrations were nominal. The 48-hour EC_{50} value, or toxic substance concentration that produced the effect of immobilization on 50% of the test population after 48 hours, was determined.
GLP:	Unknown
Test Substance:	Succinic acid, purity not specified
Results:	There was a pH drop at the 48-hour EC_{50}.
Reference:	Randall, T. L. and P. V. Knopp (1980). JWPCF, 52(8):2117-2130.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Acute Toxicity to Invertebrates: None Found

4.3 Acute Toxicity to Aquatic Plants

Type:	**Toxicity**
Species:	*Spirulina labyrinthiformis* (blue-green algae)
Value:	120 mg/L (calculated by AQUIRE staff based on data in paper)
Method:	A static test using fresh water was performed. The effect endpoint was a change in the organic process or function of the organism (photosynthesis).
GLP:	No
Test Substance:	Succinic acid, purity not specified
Results:	No additional data.
Reference:	Castenholz, R. W. et al. (1977). Microb. Ecol., 3(7):79-105

(AQUIRE/AQ-0059992).

Reliability: Low because an inappropriate method or study design was used.

Additional References for Acute Toxicity to Aquatic Plants:

Data from these additional sources were not summarized because insufficient study information was available.

Meinck, F. et al (1970). "Les eaux residuares industrielles" (cited in Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 1058, Van Nostrand Reinhold, Co., New York, NY).

Ohgai, M. et al. (1993). Bull. Jpn. Soc. Sci. Fish/Nippon Suisan Gakkaishi, 59(4):647-652 (AQUIRE/AQ-0144410).

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Study No. 1

Type: **Oral LD_{50}**
Species/Strain: Rats/Strain not specified
Value: 2260 mg/kg
Method: Either 3 or 5 male and female rats/dose were gavaged with 400,800, 1600, or 3200 mg/kg of the test substance. There was a 14-day observation period after dosing, during which rats were weighed daily. The LD_{50} was statistically calculated (method not defined).
GLP: No
Test Substance: Succinic acid, purity not specified
Results: Clinical signs of weakness and diarrhea were reported.
Reference: Eastman Kodak Co. (198 1). Unpublished Data, Report #82-0158, Health, Safety, and Human Factors Laboratory, Rochester, NY (also cited in Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3574, John Wiley and Sons, Inc., New York, NY and RTECS/WM4900000).
Reliability: Medium because a suboptimal study design was used.

Study No. 2

Type: **Oral LD_{50}**
Species/Strain: Male and female rats/ Fischer (F344)
Value: > 8 g/kg
Method: Monosodium succinate was dissolved in distilled water. Groups of 4 male and 4 female rats were given, by stomach tube, a single dose of 0.5, 1, 2, 4, or 8 g monosodium

succinate/kg body weight. The rats were observed for 10 days, and clinical signs and mortality were recorded. Thereafter all survivors were killed and examined macroscopically.

GLP: Unknown

Test Substance: Monosodium succinate, purity 100.2%

Results: In rats given 4 or 8 g monosodium succinate/kg, the only effect on the general condition of the animals was a decrease in spontaneous activity. The rats recovered from this symptom in a few days. Although 1 female rat given 8 g/kg died at week 1, all of the other rats survived until the end of the study. No clear toxicological effect was observed in rats that died or were killed, except for hemorrhage of the lungs, which was observed in some rats given the highest dose.

Reference: Maekawa, A. et al. (1990). Food Chem. Toxicol., 28(4):235-241.

Reliability: Medium because a suboptimal study design was used.

Additional Reference for Acute Oral Toxicity: None Found.

Type: **Acute Inhalation Toxicity:** No Data.

Type: **Acute Dermal Toxicity:** No Data.

Type: **Dermal Irritation**

Species/Strain: Rabbit/Strain not specified

Method: No Data

GLP: Unknown

Test Substance: Succinic acid, purity not specified

Results: Succinic acid is a slight skin irritant.

Reference: Eastman Kodak Co. (198 1). Unpublished Data, Health, Safety, and Human Factors Laboratory, Rochester, NY (cited in Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3574, John Wiley and Sons, Inc., New York, NY).

Reliability: Not assignable because limited study information was available.

Additional Reference for Dermal Irritation: None Found.

Type: **Dermal Sensitization: No** Data.

Type: **Eye Irritation**

Species/Strain: Rabbit/Albino

Method: Normal albino rabbit eyes were selected on the basis of absence of grossly visible staining using fluorescein sodium,

	flushed with distilled water 20 seconds after application. After a 2-hour interval to allow the eye to return to normal, 0.005 mL of the undiluted material was applied to the center of the cornea while the lids were retracted. About 1 minute later, the lids were released. Eighteen to 24 hours later, the eye was examined in strong, diffuse daylight, stained with fluorescein, and the injury scored.
GLP:	No
Test Substance:	Succinic acid, purity not specified
Results:	Succinic acid was a severe eye irritant, corresponding to necrosis, visible only after staining and covering about ¾ of the surface of the cornea, or a more severe necrosis covering a smaller area. It was given a grade 8 on a scale of 1 to 10.
Reference:	Carpenter, C. P. and H. F. Smyth (1946). Am. J. Onhthalmol., 29: 1363.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Eye Irritation: None Found.

5.2 Repeated Dose Toxicity

Study No. 1

Type:	**13-Week Study in Drinking Water**
Species/Strain:	Rats/Fischer (F344)
Sex/Number:	Males and females/l 0 per group
Exposure Period:	13 Weeks
Frequency of Treatment:	*Ad libitum*
Exposure Levels:	0, 0.3, 0.6, 1.25, 2.5, 5, 10%
Method:	Monosodium succinate was dissolved in distilled water, and male and female rats were given *ad libitum* the appropriate solution as their drinking water for 13 weeks. They were observed daily, and clinical signs were recorded. Body weights were measured every other week. At the end of the study, all survivors were killed for gross and microscopic examination. Hematological and biochemical examinations were also performed.
GLP:	Unknown
Test Substance:	Monosodium succinate, purity 100.2%
Results:	Severe suppression of body weight gain occurred in rats in the 10% group, and all of the rats in this group died during the 1st 4 weeks of the experiment. However, in the other dose groups all of the rats survived to the end of the experiment. Suppression of body weight gain was observed at ≥ 2.5%. The volume of drinking water consumed was very small in the highest dose groups, although it was larger

in the 5% group than in the other groups. No specific dose-related changes were observed in any parameters in the hematological and biochemical investigations.

Rats that died during the experiment were severely emaciated. However, no toxic lesions caused by the test substance were found in any organs of these rats histopathologically, although atrophy of the organs was observed. No specific lesions were observed histologically in any of the other test groups. On the basis of body weight depression, the maximum tolerated dose of monosodium succinate was determined to be approximately 2-2.5% when given in the drinking water.

Reference: Maekawa, A. et al. (1990). Food Chem. Toxicol., 28(4):235-241.

Reliability: High because a scientifically defensible or guideline method was used.

Study No. 2

Type: **2-Year Carcinogenicity Study in Drinking Water**

Species/Strain: Rats/Fischer (F344)

Sex/Number: Males and females/50 per group

Exposure Period: *2* Years

Frequency of Treatment: *Ad libitum*

Exposure Levels: 0, 1, 2%

Method: Monosodium succinate was dissolved in distilled water, and male and female rats were given *ad libitum* the appropriate solution in their drinking water for 2 years. The solutions were replaced with freshly prepared solutions 3 times/week, and the amount of solution consumed was measured to calculate the intake of the test substance. Administration of the test substance was ceased after 104 weeks and the rats were then given distilled water for a recovery period of 9 weeks. At week 113, all survivors were killed and necropsied. Animals were observed daily and clinical signs and mortality were recorded. Body weights were measured once/week for the first 13 weeks, then once every 4 weeks. All rats that died or were killed when moribund during the study and all those killed at the end of the study were necropsied completely and examined macro- and microscopically for the presence of non-neoplastic and neoplastic lesions. All lesions and organs and/or tissues were routinely fixed, sectioned, and stained.

GLP: Unknown

Test Substance: Monosodium succinate, purity 100.2%

Results: Throughout the experiment, a dose-dependent inhibitory effect on growth was apparent in both sexes. In **males,** the mortality rate in the control group was slightly higher than that in the other 2 groups throughout the experiment. In males, the overall tumor incidence was almost 100% in all groups. In females, it was approximately 77-82%. In both sexes, there were no statistically significant differences between the control and treated groups in overall tumor incidences and mean survival times.

Tumors were found in many organs or tissues in all groups including the controls. In males of all groups, tumors of the testes were the most frequent, followed by those of the hematopoietic organs, thyroid, adrenals, mammary, prostate, pancreas, and pituitary. Tumors of the uterus, pituitary, hematopoietic organs, mammary gland, thyroid, and adrenals were the most common in females. Tumors were also detected in other organs or tissues, but the incidences were very low. None of the treated groups showed a significant increase in the incidence of any tumors over that in the corresponding controls, while the incidence of endometrial stromal polyp in the females given the 2% dose was significantly lower than that in the control group. The incidence of C-cell adenoma/carcinoma of the thyroid in the females given 2% was higher than that in the controls, although marginally not significant, and a positive trend was noted in the occurrence of this tumor by an age-adjusted statistical test. Histologically, all tumors, except prostate tumors, observed in this study were similar to those that are known to occur spontaneously in this strain of rats. Prostate tumors were observed in all male groups, including the control group, at incidences much higher than those reported by others. Histologically, the prostate tumors were all intraductal adenomas/carcinomas. In addition to these tumors, many kinds of non-neoplastic lesions, such as myocardial fibrosis, bile duct proliferation, and chronic nephropathy were observed in all groups including controls, and no other specific lesions were detected in any treated groups of either sex.

From the above result, it was concluded that monosodium succinate had no carcinogenic activity in F344 rats when given continuously in the drinking water for 2 years.

Reference: Maekawa, A. et al. (1990). Food Chem. Toxicol., 28(4):235-241.

Reliability: High because a scientifically defensible or guideline method

was used.

Additional References for Repeated Dose Toxicity:

Data from these additional sources were not summarized because insufficient study information was available.

Dye, W. S. et al. (1944). Growth, 8:1-11.

Eastman Kodak Co. (198 1). Unpublished Data, Health, Safety, and Human Factors Laboratory, Rochester, NY (cited in Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3574, John Wiley and Sons, Inc., New York, NY).

Friend, V. L. and H. Cold (1947). J. Am. Pharm. Assoc., 36:50.

Thind, S. K. et al. (1980). Indian J. Med. Res., 71:611 (cited in Clayton, G. D. and F. E. Clayton (1994). Patty's Industrial Hygiene and Toxicology, 3rd ed., Vol. II, p. 3574, John Wiley and Sons, Inc., New York, NY).

5.3 Developmental Toxicity: No Data.

Additional References for Developmental Toxicity:

Data for these additional sources were not summarized because the study design was not adequate.

Verrett, M. J. et al. (1980). Toxicol. Appl. Pharmacol., 56:265-273.

Dye, W. S. et al. (1944). Growth, 8:1-11.

Ain, R. and P. B. Seshagiri (1997). Mol. Reprod. Dev., 47(4):440-447.

Barilyak, I. R. et al. (1980). Deposited Doc., VINITI 1357-80 (CA95:18285).

5.4 Reproductive Toxicity:

Species/Strain:	Rats/Strain not specified
Sex/Number:	Females/40 (30 test animals and 10 controls)
Route of Administration:	Injection
Exposure Period:	3 weeks
Frequency of Treatment:	Daily
Exposure Levels:	5.0 mg/day
Method:	Daily vaginal smears were made on 40 rats for 2 weeks. At

	the end of the 2 weeks, 30 of the rats were ovariectomized. A post-operative period of 7 days was allowed to elapse before injections were started. Vaginal smears were continued to confirm the expected diestrus smear following ovariectomy. The rats were injected subcutaneously for 3 weeks. Daily vaginal smears were made. At the end of the 3-week injection period, all animals were sacrificed and microscopic sections were made of the uterine horn, cervix, and vagina.
GLP:	No
Test Substance:	Succinic acid, purity not specified
Results:	Daily vaginal smears showed no change from the diestrus smear of ovariectomized rats as compared to the typical 4-day cyclic changes in the vaginal smears of the controls. Microscopic sections of the uterine horn, cervix, and vagina of each of the rats showed no significant changes.
Reference:	Dye, W. S. et al. (1944). Growth, 8: 1-11.
Reliability:	Inadequate because an inappropriate method or study design was used.

Additional References for Reproductive Toxicity: None Found.

5.5 Genetic Toxicity

Type:	***In vitro* Reverse Mutation Assay**
Bacterial Tester Strains:	*Salmonella typhimurium* TA92, TA1535, TA100, TA1537, TA94, and TA98
Exogenous Metabolic Activation:	With and without polychlorinated biphenyl KC-400-treated rat liver S-9
Exposure Concentrations:	Maximum dose of 5.0 mg/plate; no other doses specified.
Method:	Reverse mutation assays were carried out according to the pre-incubation method of Ames et al., 1975. Cells cultured overnight were pre-incubated with both the test substance and the S-9 mix for 20 minutes at 37°C before plating. Duplicate plates were used for each of 6 different concentrations of the sample. The number of revertant (his+-) colonies was scored after incubation at 37°C for 2 days. The result was considered positive if the number of colonies found was twice the number in the control (phosphate buffer).
GLP:	Unknown
Test Substance:	Succinic acid, purity 100.4%
Results:	Negative
Remarks :	Succinic acid was not mutagenic to *Salmonella typhimurium*

	TA92, TA1535, TA100, TA1537, TA94, and TA98, with and without polychlorinated biphenyl KC-400-treated rat liver S-9 at a maximum dose of 5.0 mg/plate (no other doses were specified). No significant increases in the number of revertant colonies were detected in any S. *typhimurium* strains at the maximum dose.
Reference:	Ishidate, M., Jr. et al. (1984). Food Chem. Toxicol., 22(8):623-636.
	Ames, B. N. et al. (1975). Mutat. Res., 31:347-364.
Reliability:	Medium because a suboptimal study design was used.

Additional References for *In vitro* Reverse Mutation Assay:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Litton Bionetics, Inc. (1975). LBI Project No. 2468 (NTIS PB254-519).

Khudoley, V. V. et al. (1987). Arch. Geschwulstforch., 57:453-462.

Type:	**Chromosomal Aberration Test**
Cell Type:	Chinese hamster fibroblasts
Exogenous Metabolic Activation:	Without metabolic activation
Exposure Concentrations:	Maximum dose: 1 .O mg/mL; no other doses were specified.
Method:	The cells were exposed to the test substance at 3 different doses for 24 and 48 hours. The maximum dose was selected based on a preliminary test, in which the dose needed for 50% cell-growth inhibition was estimated using a cell densitometer. Chromosome preparations were made as follows: colcemid was added to the culture 2 hours before cell harvesting, the cells were then treated with a hypotonic KC1 solution, fixed, spread on clean glass slides, air dried, and stained with Giemsa. A hundred well-spread metaphases were analyzed under the microscope. The incidence of polyploid cells, as well as of cells with structural chromosomal aberrations was recorded. Untreated cells and solvent-treated (physiological saline) cells served as negative controls. The results were considered to be negative if the incidence was less than 4.9%, equivocal if it was between 5.0 and 9.9%, and positive if it was more than 10.0%. (Note: Metabolic activation was not employed.)

GLP:	Unknown
Test Substance:	Succinic acid, purity 100.4%
Results:	Negative
Remarks:	There was 0% polyploid and 1 .O% structural aberrations at 48 hours at the maximum dose tested.
Reference:	Ishidate, M., Jr. et al. (1984). Food Chem. Toxicol., 22(8):623-636.
Reliability:	Medium because a suboptimal study design was used, and limited study information was available.

Additional References for *In* vitro Clastogenicity Studies:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Heindorff, K. et al. (1984). Mutat. Res., 140:123-126.

Data from this additional source were not summarized because insufficient study information was available.

Nago, M (1978). Mutagens and Carcinogens. Protein, Nucleic Acid. and Enzyme, 23:435-447 (cited in Yanagisawa, K. et al. (1987). Mutat. Res., 183:89-94).

Type: ***In vivo*** **Genetic Toxicity:** No Data.

Appendix D

10-July-2001

ROBUST SUMMARY FOR DIBASIC ACID MIXTURE

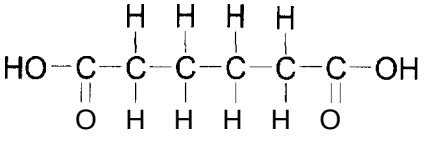
The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as related references in this document.

1.0 Substance Information

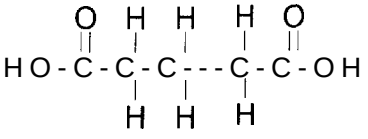
CAS Number: No Data

Chemical Name: Hexanedioic acid, mixt. with butanedioic acid and pentanedioic acid

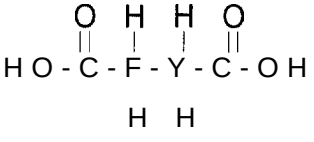
Structural Formula:



Adipic acid



Glutaric acid



Succinic acid

Other Names: Anhydrous dibasic acid (adipic/glutaric/succinic)
DBA dibasic acid mixture
Dicarboxylic acids mixture
DBA
Solid DBA dibasic acid
DBA mixture anhydrous
Dibase III dicarboxylic acids mixture

Exposure Limits: No Data.

2.0 Physical - Chemical Properties

2.1 Melting Point:

Value:	100-130°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	BASF AG (1990). Safety Data Sheet, Dicarbonsäuregemisch Dest. (10/90) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxvlic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).
Reliability:	Not assignable because limited study information was available.

Additional References for Melting Point: None Found.

2.2 Boiling Point:

Value:	300-330°C
Decomposition:	No Data
Pressure:	1013 hPa
Method:	No Data
GLP:	Unknown
Reference:	BASF AG (1990). Safety Data Sheet, DICARBONSÄUREGEMISCH DEST. (1 0/90) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxvlic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point: None Found.

2.3 Density

Value:	1.23 g/cm^3
Temperature:	20°C
Method:	DIN 51757
GLP:	Unknown
Results:	Bulk density = ca. 530 kg/m^3 @ 20°C; DIN IS0 787
Reference:	BASF AG (1990). Safety Data Sheet, DICARBONSÄUREGEMISCH DEST. (10/90) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxvlic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Reliability:	Not assignable because limited study information was available.

Additional References for Density:

BASF AG (1990). Safety Data Sheet, SOKALAN DCS (3/90) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

DuPont Co. (1996). Material Safety Data Sheet No. 34410098.

2.4 Vapor Pressure

Value:	4 mm Hg
Temperature:	160°C
Decomposition:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1996). Material Safety Data Sheet No. 34410098.
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure:

BASF AG (1990). Safety Data Sheet, SOKALAN DCS (3/90) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (n.d.). Analytical Laboratory; unpublished study (BRU 74/34) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

2.5 Partition Coefficient (log Kow): No Data.

2.6 Water Solubility

Value:	35 wt% (350 g/L)
Temperature:	25°C
pH/pKa:	No Data
Method:	No Data
GLP:	Unknown
Reference:	DuPont Co. (1996). Material Safety Data Sheet No. 34410098.
Reliability:	Not assignable because limited study information was available.

Additional Reference for Water Solubility:

BASF AG (1990). Safety Data Sheet, DICARBONSAUREGEMISCH DEST. (10/90) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxvlic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

2.7 Flash Point:

Value:	232°C
Method:	Closed cup
GLP:	Unknown
Reference:	DuPont Co. (1996). Material Safety Data Sheet No. 34410098.
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point:

BASF (1983). Data, Data sheet Dicarbonsaeuregemisch (November) (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (1990). Safety Data Sheet, DICARBONSAUREGEMISCH DEST. (10/90) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxvlic acids [October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Bayer AG (1992). Safety Data Sheet from 25.06.1992 (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

2.8 Flammability: No Data.

3.0 Environmental Fate

3.1 Photodegradation: No Data.

3.2 Stability in Water: No Data.

3.3 Transport (Fugacity): No Data.

3.4 Biodegradation:

Value :	Degradation after 7 days was 99% (based on DOC). In the Zahn-Wellens test, 5% degradation was observed after 3 hours. The concentration was 400 mg/L.

Breakdown Products:	No Data
Method:	Zahn-Wellens test, DIN 38412, Part 25 (static test), OECD Guideline 302B, updated 7/85, IS0 DP 9888, EEC Directive 88/302/EEC, Part C in the Official Journal of the European Communities L133 of 30.05.1988.
GLP:	Unknown
Reference:	BASF AG (1988). Ecology Lab., unpublished study (report from 29.11.88) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxvlic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).
Reliability:	Medium because a suboptimal study design was used and limited study information was available.

Additional Reference for Biodegradation:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

BASF AG (1988). Ecology Lab., unpublished study (report from 29.11.88) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxvlic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

3.5 Bioconcentration: No Data.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish:

Study No. 1

Type:	**96-hour static LC_{50}**
Species:	Rainbow trout (*Oncorhynchus mykiss*)
Value:	**240** mg/L
Method:	Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians, USEPA, 1975.

Fish were obtained from the commercial fish hatchery, Spring Creek Trout Hatchery, in Lewistown, Montana. Fish were held in a culture tank with a 16-hour daylight photoperiod for 14 days prior to testing. Ten fish were added to each test vessel, which was kept in a water bath maintained at 12°C. Food was withheld for 48 hours prior to testing. Fish had a mean weight of 0.42 g and a mean length of 3 1 mm. Water quality was measured at the beginning, 48-hour, and 96-hour periods and included DO, pH, and temperature.

GLP:	Yes
Test Substance:	Dicarboxylic acids, purity not specified
Results:	All results were based on the nominal concentrations of 100, 180, 320, 560, and 1000 mg/L. The NOEC (no-observed-effect-concentration) value was based on mortality and lack of abnormal behavior. The fish were challenged in a reference compound test using Antimycin A to verify that the fish were responding acceptably. Results were consistent with values reported in literature. pH values ranged from 7.4 to 3.7 with the lowest pH values being observed at the highest test concentrations where survival was lowest. pH levels were considered adequate for testing. Dissolved oxygen ranged from 9.0 to 6.8 mg/L representing 83% to 63% saturation (2 1°C) and were considered adequate for testing. The NOEC level was 180 mg/L.
Reference:	Solutia Inc. (1983). Unpublished Data, ABC Laboratory (30442) performed for Monsanto, Monsanto Number AB-83-136.
Reliability:	High because a scientifically defensible or guideline method was used.

Study No. 2

Type:	**96-hour static LC_{50}**
Species:	Bluegill sunfish (*Lepomis macrochirus*)
Value:	340 mg/L
Method:	Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians, USEPA, 1975. Fish were obtained from the commercial fish hatchery, Fattig Fish Hatchery, in Brady, Nebraska. Fish were held in a culture tank with a 16-hour daylight photoperiod for 14 days prior to testing. Ten fish were added to each test vessel, which was kept in a water bath maintained at 22°C. Food was withheld for 48 hours prior to testing. Fish had a mean weight of 0.21 g and a mean length of 23 mm. Water quality was measured at beginning, 48-hour, and 96-hour periods and included DO, pH, and temperature.
GLP:	Yes
Test Substance:	Dicarboxylic acids, purity not specified
Results:	All results were based on the nominal concentrations of 100, 180, 320, 560, and 1000 mg/L. The NOEC value was based on mortality and lack of abnormal behavior. After 72 hours of testing, all test concentrations with live fish (100, 180, and 320 mg/L) had become hazy. The fish were challenged in a

reference compound test using Antimycin A to verify that the fish were responding acceptably. Results were consistent with values reported in literature. pH values ranged from 7.4 to 3.7 with the lowest pH values being observed at the highest test concentrations where survival was lowest. pH levels were considered adequate for testing. Dissolved oxygen ranged from 9.2 to 3.4 mg/L representing 102% to 38% saturation (2 1°C) and were considered adequate for testing.

The NOEC level was 180 mg/L.

Reference: Solutia Inc. (1983). Unpublished Data, ABC Laboratory (30442) performed for Monsanto, Monsanto Number AB-83-136.

Reliability: High because a scientifically defensible or guideline method was used.

Additional Reference for Acute Toxicity to Fish:

Data from this additional source were not summarized because insufficient study information was available.

BASF AG (n.d.). Toxicology Department; unpublished study (79/556) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

4.2 Acute Toxicity to Invertebrates:

Type: **48-hour static EC_{50}**

Species: *Daphnia magna*

Value: > 1000 mg/L

Method: Methods for Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians, USEPA, 1975.

Daphnia were cultured at ABC Laboratory facilities. Test vessels were kept at 20°C in a temperature controlled area. Lighting was maintained at 50-70 foot-candles on a 16-hour photoperiod. Ten organisms per vessel were used and each concentration was performed in duplicate. Water quality was measured at the beginning, 48-hour, and 96-hour periods and included DO, pH, and temperature.

GLP: Yes

Test Substance: Dicarboxylic acids, purity not specified

Results: All results were based on the nominal concentrations of 100, 180, 320, 560, and 1000 mg/L. The NOEC value was based on mortality and lack of abnormal behavior. pH values

ranged from 7.8 to 8.5, and were considered adequate for testing. Dissolved oxygen ranged from 6.7 and 7.5 mg/L representing 73% to 82% saturation (20°C) and was considered adequate for testing.

The NOEC level was 1000 mg/L.

Reference: Solutia Inc. (1983). Unpublished Data, ABC Laboratory (30442) performed for Monsanto, Monsanto Number AB-83-136.

Reliability: High because a scientifically defensible or guideline method was used.

Additional Reference for Acute Toxicity to Invertebrates:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

BASF AG (n.d.). Ecology Lab., unpublished study (0814/88) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

4.3 Acute Toxicity to Aquatic Plants:

Type: **96-hour EC_{50}**
Species: *Scenedesmus subspicatus*
Value: 35 mg/L
Method: Cell multiplication inhibition test, DIN 38412, Part 9, Determination of inhibitive effect of water pollutants on green algae.
GLP: Unknown
Test Substance: Dicarboxylic acids, purity not specified
Results: The 96-hour EC_{10} was 19 mg/L. The determination of biomass at 96 hours for EBC_{10} and EBC_{50} were 6.5-55 mg/L and 13-93 mg/L, respectively. The 72-hour EC_{10} and EC_{50} were 49 and 66 mg/L, respectively. The determination of biomass at 72 hours for EBC_{10} and EBC_{50} were 25-95 mg/L and 36-12 1 mg/L, respectively. At 72 hours, at concentrations of 10, 50, and 100 mg/L the initial respective pH values were 7.84, 5.68, and 4.48.
Reference: BASF AG (n.d.). Ecology Lab., unpublished study (0814/88) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).
Reliability: Medium because a suboptimal study design was used and limited study information was available.

Additional References for Acute Toxicity to Aquatic Plants: None Found.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral LD_{50}**
Species/Strain:	Rats/Crl:CD®
Value:	6829 mg/kg
Method:	The test substance, as an aqueous solution, was administered by intragastric intubation in single doses to 4 groups of 10 young adult male rats. The surviving rats were weighed and observed during a 14-day recovery period, and then sacrificed. The LD_{50} value was calculated using the method of D. J. Finney.
GLP:	No
Test Substance:	Dicarboxylic acids, purity 99.5%
Results:	Mortality was 0/10, 3/10, 5/10, and 6/10 at 5000, 6000, 6500, and 7500 mg/kg, respectively. All deaths occurred within 5 days after dosing. Clinical signs observed included weight loss (all levels), stained face (≥ 6000 mg/kg), stained perineal area (6000 mg/kg), weakness (≥ 6500 mg/kg), chromodacryorrhea (6000 and 7500 mg/kg), and congestion (5000 and 6500 mg/kg).
Reference:	DuPont Co. (I 982). Unpublished Data, Haskell Laboratory Report No. 562-82.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Acute Oral Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Solutia Inc. (1978). Unpublished Data, YO-78-273.

BASF (1983). Data, Data sheet Dicarbonsaeuregemisch (November) (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF (n.d.). Data, Ergebnis der gewerbetoxikologischen Grundpruefung, Substanz-Nr. 77/426. BASF AG, Gewerbehygiene und Toxikologie, Ludwigshafen, 7 S. (cited in BUA (1993). BUA Reuort 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (n.d.). Toxicology Department, unpublished study (XXII/3 18) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (n.d.). Toxicology Department, unpublished study (77/426) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

DuPont Co. (1980). Unpublished Data, Haskell Laboratory Report No. 836-80.

Data from this additional source were not summarized because the study design was not adequate.

Harnisch, S. (1977). Arch. Gefluegelkd., 41(3):103-104 (CA87:116817x).

Type:	**Inhalation LC_{50}**
Species/Strain:	Rat/Strain not specified
Exposure Time:	4 hours
Value:	> 0.03 mg/L
Method:	The maximum concentration technically feasible was tested; analytical concentration.
GLP:	unknown
Test Substance:	Dicarboxylic acids, purity ≥ 97%
Results:	Mortality was 0/20.
Reference:	BASF (1983). Data, Data sheet Dicarbonsaeuregemisch (November) (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart). BASF (1979). Data, Bericht ueber die Bestimmung der akuten Inhalationstoxizitaet LC50 von Sokalan DCS bei 4-stuendiger Exposition an Sprague-Dawley-Ratten, 02.03.1979. BASF AG, Gewerbehygiene und Toxikologie, Ludwigshafen, 6 S. (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart). BASF (n.d.). Toxicology Department, unpublished study (77/426) (cited in BUA (1992). BUA Report 137: C4-6. Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).
Reliability:	Medium because a suboptimal study design was used and limited study information was available.

Additional References for Acute Inhalation Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

BASF (n.d.). Data, Ergebnis der gewerbetoxikologischen Grundpruefung, Substanz-Nr. 77/426. BASF AG, Gewerbehygiene und Toxikologie, Ludwigshafen, 7 S. (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF (1983). Data, Data sheet Dicarbonsaeuregemisch (November) (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Type:	**Dermal LD_{50}**
Species/Strain:	Rabbit/New Zealand White
Value:	> 7940 mg/kg
Method:	Method followed OECD Guideline 402 "Acute dermai Toxicity." The estimate of minimum lethal dose was based on a 24-hour exposure, with an occluded patch, and a 14-day observation period. Necropsy was performed on animals that died as well as survivors.
GLP:	No. Test was conducted consistent with US GLPs effective 6/79.
Test Substance:	Dicarboxylic acids (tested as a 40% aqueous solution of concentrate), purity not specified
Results:	Mortality ratios of O/l and 0/2 were observed at 50 10 mg/kg and 7940 mg/kg, respectively. Weight loss was observed at 2-4 days on test. No effects on viscera were noted.
Reference:	Solutia Inc. (1978). Unpublished Data, YO-78-273.
Reliability:	Medium because a suboptimal study design was used.

Type:	**Dermal LD_{50}**
Species/Strain:	Rat/Strain not specified
Value:	> 200 mg/kg
Method:	No Data
GLP:	Unknown
Test Substance:	Dicarboxylic acids, purity ≥ 97%
Results:	No Data
Reference:	BASF AG (n.d.). Data, Ergebnis der gewerbetoxikologischen Grundpruefung, Substanz-Nr. 77/426. BASF AG, Gewerbehygiene und Toxikologie, Ludwigshafen, 7 S. (cited in BUA (1993). BUA Report 136:

Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF (1983). Data, Data sheet Dicarbonsaeuregemisch (November) (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (n.d.). Toxicology Department, unpublished study (77/426) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Reliability: Medium because a suboptimal study design was used and limited study information was available.

Additional References for Acute Dermal Toxicity: None Found.

Type:	**Dermal Irritation**
Species/Strain:	Guinea pigs/Duncan Hartley
Method:	The test substance, 0.05 mL of an 80% and an 8% suspension in dimethyl phthalate (DMP), was applied and lightly rubbed on to the shaved, intact shoulder skin of 10 male guinea pigs. Evaluations were made after 24 and 48 hours.
GLP:	No
Test Substance:	Anhydrous dibasic acids, purity 87%
Results:	An 80% suspension of the test substance produced mild to no irritation at 24 hours. There was no irritation at 48 hours. As an 8% suspension, no irritation resulted at 24 or 48 hours.
Reference:	DuPont Co. (1980). Unpublished Data, Haskell Laboratory Report No. 837-80.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

BASF (1977). Data, Ergebnis der gewerbetoxikologischen Grundpruefung, Substanz-Nr. 77/426. BASF AG, Gewerbehygiene und Toxikologie, Ludwigshafen, 7 S. (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF (1983). Data, Data sheet Dicarbonsaeuregemisch (November) (cited in

BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (n.d.). Toxicology Department, unpublished study (771426) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (n.d.). Toxicology Department, unpublished study (XXII/3 18) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Data from this additional source were not summarized because the focus of the study was skin corrosion.

DuPont Co. (1986). Unpublished Data, Haskell Laboratory Report No. 232-86.

Type:	**Dermal Sensitization**
Species/Strain:	Guinea pigs/Duncan Hartley
Method:	A test for primary irritation was conducted by applying, and lightly rubbing in, approximately 0.05 mL of a 80% and 8% suspension of the test substance in dimethyl phthalate (DMP) on the shaved intact shoulder skin of 10 male guinea pigs. To test for the sensitization potential, a series of 4 sacral intradermal injections was given, 1 each week beginning 2 days after the test for primary irritation, which consisted of 0.1 mL of a 1.0% suspension of the test substance in DMP. After a 13-day rest period, the test animals were challenged for sensitization by applying, and lightly rubbing in, approximately 0.05 mL of an 80% and 8% suspension of the test substance in DMP on the shaved intact shoulder skin. At the same time, 10 previously unexposed guinea pigs of the same age received similar topical applications, and served as control animals.
GLP:	No
Test Substance:	Anhydrous dibasic acids, purity 87%
Results:	Refer to Dermal Irritation for results of the primary irritation phase of this study. At challenge, no sensitization was observed at 80% or 8%.
Reference:	DuPont Co. (1980). Unpublished Data, Haskell Laboratory Report No. 837-80.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Dermal Sensitization: None Found.

Type:	**Eye Irritation**
Species/Strain:	Rabbits/Albino
Method:	One-tenth mL (44.3 mg) of solid test substance was placed into the right conjunctival sac of each of 2 male rabbits. After 20 seconds, 1 treated eye was washed with tap water for 1 minute. The treated eye of the other rabbit was not washed. Observations of the cornea, iris, and conjunctiva were made with an ophthalmoscope at 1 and 4 hours, and 1, 2, 3, 7, 14, and 21 days. Fluor-i-strip® stain and a slit-lamp biomicroscope were used at examinations after the day of treatment.
GLP:	No
Test Substance:	Anhydrous dibasic acids, purity 87%
Results:	A generalized area of moderate cloudiness with swelling in the stroma area, moderate iritis, and mild to severe conjunctivitis were observed in both the washed and unwashed rabbit eyes. Both eyes were normal within 21 days.
Reference:	DuPont Co. (1980). Unpublished Data, Haskell Laboratory Report No. 835-80.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Eye Irritation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

BASF (1977). Data, Ergebnis der gewerbetoxikologischen Grundpruefung, Substanz-Nr. 77/426. BASF AG, Gewerbehygiene und Toxikologie, Ludwigshafen, 7 S. (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF (1983). Data, Data sheet Dicarbonsaeuregemisch (November) (cited in BUA (1993). BUA Report 136: Glutaric Acid (April), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (n.d.). Toxicology Department, unpublished study (77/426) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

BASF AG (n.d.). Toxicology Department, unpublished study (XXII/3 18) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

5.2 Repeated Dose Toxicity:

Type:	**90-Day Oral Gavage Study**
Species/Strain:	Rat/Sprague-Dawley
Sex/Number:	Male and female/l 5 per sex per test group
Exposure Period:	90 days
Frequency of Treatment:	Daily
Exposure Levels:	0, 3, 10, 30% (0, 300, 1000, 3000 mg/kg)
Method:	OECD Guideline 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"
	The vehicle used was deionized water and the dosing volume was 10 mL/kg.
	Mortality, moribundity, and toxic signs were recorded daily. Body weight and food consumption were recorded weekly.
	The following parameters were measured/calculated on 10 rats/sex/group at 13 weeks: hematology (mct, hgb, rbc, mch, mcv, mchc, t. & diff. leuko, pltlets, retic), blood chemistry (AST, ALT, SAP, Glu, BUN, T. Bili, T. chol, Alb, Glob, T. prot., Creat, Na, K, Cl, Ca, Phos, GGT, OCT, CPK), and urinalysis (vol, pH, S. Grav, prot, glu, ket, urobil, nitriles, bili, occ. bld, sedim).
	The following parameters were conducted on all animals at 13 weeks: ophthalmoscopic exam, organ weights and ratios (liver, kidney, heart, adrenal, ovaries, testes, brain), and necropsy. Histopathology of over 45 tissues and organs was conducted on all high dose and control animals.
GLP:	Yes
Test Substance:	Dicarboxylic acids, 4% adipic, 16% glutaric, 5% succinic, and up to 4% nitric
Results:	At the 30% level, deaths of 2/15 males and 1/15 females were judged treatment-related. Body weights were reduced in males (10%) and females (5.5%), and statistically significant reductions in food consumption were observed in the males only. Males and females at this level also had an increased incidence of labored breathing and rales. Statistically increased leukocytes were found in males (segmented neutrophils and lymphocytes slightly elevated), and urine pH was statistically reduced in the 30% male and female groups.

At the 10% dose level, clinical signs were less prominent. The urine pH was reduced in males only. Body weight gain (not statistically significant) was slightly reduced in females only, and food consumption was statistically reduced in males only.

At the 3% dose level there were no effects. There were no histopathology or weight effects at any test level.

The NOAEL was 3% and the LOAEL was 10%.

Reference: Solutia Inc. (1983). Unpublished Data, IR-83-142.

Reliability: High because a scientifically defensible or guideline method was used.

Additional Reference for Repeated Dose Toxicity:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Solutia Inc. (1983). Unpublished Data, IR-83-14 1.

5.3 **Developmental Toxicity:** No Data.

5.4 **Reproductive Toxicity:** No Data.

5.5 **Genetic Toxicity:**

Type: **In vitro Bacterial Reverse Mutation Assay**

Tester Strains: *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538

Exogenous Metabolic Activation: With and without Aroclor 1254-induced rat liver S-9

Exposure Concentrations: 0, 30, 100, 300, 1000, 3000 µg/plate

Method: OECD Guideline 47 1 "Genetic Toxicology: *Salmonella typhimurium* Reverse Mutation Assay"

Triplicate analyses were conducted with deionized water as the solvent. Data were analyzed via linear regression analysis ($p<0.05$). Positive controls used in the study included 2-anthramine, 9-aminoacridine, 2-nitrofluorene, and sodium azide.

GLP: Yes

Test Substance: Dicarboxylic acids (tested as a 50% aqueous solution), purity

	not specified
Results:	Negative
Remarks:	The cytotoxic concentration was 5000 µg/plate (absence of lawn) determined in a pretest screen. The 1"' test of TA1538 exhibited a 2.5-fold increase in mutants versus control only at 30 µg/plate without S-9. The 2 retests did not confirm the original observation. No statistically significant increases occurred at any other test level for any tester strains. The solvent control and positive controls responded adequately.
Reference:	Solutia Inc. (1985). Unpublished Data, PK-85-305.
Reliability:	High because a scientifically defensible or guideline method was used.
Type:	**In *vitro* Cytogenetic Assay**
Tester Strains:	CHO cells, strain A-l for original assay and JSS-1 for confirmatory test
Exogenous Metabolic Activation:	With and without Aroclor 1254-induced rat liver S-9
Exposure Concentrations:	0, 100,750, 1000, 1500 µg/mL without S-9 0,200, 800, 2000, 2500 µg/mL with S-9
Method:	Directive 87/302/EEC, part B, p. 73 "Mutagenicity: - *In vitro* mammalian cell transformation tests" Duplicate tests were conducted. Fifty metaphases per dose were analyzed statistically by Chi-square analysis for group cells with aberrations and t-test for aberrations/cell ($p<0.05$). Distilled water was used as the solvent. N-methyl-N'-nitro-N-nitrosoguanidine and dimethylnitrosamine were used as positive controls.
GLP:	Yes
Test Substance:	Dicarboxylic acids (tested as a concentrate), purity not specified
Results:	Positive with, but not without, metabolic activation
Remarks:	The cytotoxic concentration was 2500 µg/mL with S-9 and 1500 µg/mL without S-9. Both of these concentrations produced no survival of cells. A positive response was observed at 2000 µg/mL with S-9. The confirmatory study run with S-9 at 1500, 2000, and 2200 µg/mL confirmed the positive response. When tested without S-9 metabolic activation, no positive response was observed.
Reference:	Solutia Inc. (1985). Unpublished Data, PK-85-306.
Reliability:	High because a scientifically defensible or guideline method was used.

Type:	***In* vitro DNA Damage and Repair Assay**
Tester Strains:	F344 rat hepatocytes
Exposure Concentrations:	10, 50, 100, 500, 1000, 2500 µg/mL
Method:	Triplicate trials were conducted with 150 cells/concentration/trial evaluated for unscheduled DNA synthesis (UDS). Frequency distribution of net, average, and median grain counts were calculated and compared to the untreated control. 2-Acetyl aminofluorene was used as the positive control.
GLP:	Yes
Test Substance:	Dicarboxylic acids, purity not specified
Results:	Negative
Remarks :	The cytotoxic concentration was 5000 µg/mL. Acidity was noted at 50-2500 µg/mL. No increase in UDS was observed at any test level.
Reference:	Solutia Inc. (1985). Unpublished Data, SR-85-308.
Reliability:	High because a scientifically defensible or guideline method was used.

Type:	***In* vitro HGPRT Assay**
Tester Strains:	CHO-K1-BH4
Exogenous Metabolic Activation:	With and without Aroclor 1254-induced rat liver S-9
Exposure Concentrations:	1500, 1750, 2000, 2250, 2500 µg/mL without S-9 1500, 2000, 2500, 3000, 3500 µg/ml with 10% S-9
Method:	Triplicate assays were conducted. Ethyl methanesulphonate and dimethylnitrosamine were used as positive controls. Statistical analysis on transformed data was by l-way ANOVA.
GLP:	Yes
Test Substance:	Dicarboxylic acids, purity not specified
Results:	Negative
Remarks :	No statistically significant differences were observed. All positive and negative controls were acceptable.
Reference:	Solutia Inc. (1985). Unpublished Data, PK-85-307.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for *In Vitro* Genetic Toxicity:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

BASF AG (n.d.). Toxicology Department, unpublished study (89/891) (cited in BUA (1992). BUA Report 137: C4-6 Dicarboxylic acids (October), S. Hirzel, Wissenschaftliche Verlagsgesellschaft Stuttgart).

Type:	***In vivo* Cytogenetic Assay**
Species/Strain:	Rat/ Sprague-Dawley
Sex/Number:	Male and female/8 males at 6 hours, 5 males at 18 and 30 hour intervals and 5 females/interval
Route of Administration:	Gavage; single dose and sacrificed 6, 18, or 30 hours later
Concentrations:	2750 mg/kg (males) 1375 mg/kg (females)
Method:	Fifty metaphase bone marrow ceils/animal were evaluated. Cyclophosphamide was used as the positive control. One-tail T test of 50 cells/rat were conducted. Statistical evaluation for aberrations and group mean aberrations/cell were compared by Chi-square ($p<0.05$).
GLP:	Yes
Test Substance:	Dicarboxylic acids (tested as a concentrate), purity not specified
Results:	Negative
Remarks:	An MTD (maximum tolerated dose) was reached or even exceeded based on deaths at the top dose. Three males died at 2750 mg/kg. No females (0/15) died at 1375 mg/kg. Toxic signs noted included decreased activity, ptosis, abnormal gait or stance, tremors, piloerection, decreased body tone, and vocal to touch in the males and decreased activity, decreased body tone, piloerection, and vocal at touch in the females.
Reference:	Solutia Inc. (1988). Unpublished Data, PK-88-345.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for *In Vivo* Genetic Toxicity: None Found.